AWARD NUMBER: W81XWH-12-1-0352

TITLE: Tribosupplementation with Lubricin in Prevention of Post-Traumatic Arthritis

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REPORT DATE: October 2014

TYPE OF REPORT: Annual Report

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

DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited

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Full length recombinant human lubricin (rhPRG4) maximally reduced friction between apposed explants of bovine articular cartilage. Secretion levels exceeded 1 mg/ml when expressed by transfected CHO-M cells. This level of expression is commercially scalable and will thus enable production of a GMP protein for clinical use. A purification bioprocess utilizing anion exchange, hydroxyapatite and a hydrophobic exchange media resins achieves a high level of purity. Explants of bovine articular cartilage cultured and incubated with IL-1 followed by friction testing showed higher friction than explants not receiving IL-1. The rhPRG4 restored low friction and qualitatively restored native PRG4 expression as determined by immunohistochemistry. Cartilage from the femoral condyle shows variations in IL-1 induced elevated friction. Explants from the weight bearing region show a significant response to exogenous rhPRG4 in friction reduction from this simulated inflammatory environment. A large animal trial is now planned to test pre-GMP equivalent rhPRG4 in restoring chondroprotection in the ACL-injured joint.
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INTRODUCTION
We have produced recombinant human lubricin (rhPRG4), which we hypothesized would provide disease modifying relief to patients at risk for post-traumatic OA of the knee. The epidemiologic civilian experience indicates that 18% of the total OA burden is of traumatic origin. Among military servicemen and women, acute knee injuries comprise almost 5% of all reported injuries. Intra-articular (IA) injections of recombinant lubricin in pre-clinical rodent models show a chondroprotective effect upon cartilage structure and chondrocyte metabolism. Lubricin is a mucinous glycoprotein which we show can be manufactured by CHO-M cells. The point of this work was also to establish that the production of this recombinant human protein is scalable to levels required for the treatment of patients. We have identified a bioprocess for purification and have ascertained that the recombinant protein is active in an in vitro cartilage explant bearing system. We have identified a candidate recombinant lubricin that possesses scalability and maximal chondroprotective bioactivity in the form of low friction. We have also reproduced this result in a cartilage explant stimulated with IL-1 to induce cartilage damage. We are presently testing this rhPRG4 for its ability to diminish caspase-3 activity in chondrocytes which will confirm its friction-reducing activity in vitro. This candidate will undergo clonal expansion. Enough lubricin has been purified to enable a trial in swine to determine if intra-articular injection of lubricin minimizes cartilage damage following ACL transection, and in another cohort after ACL reconstruction, the current gold standard that does not minimize cartilage loss. All of the reagents and cell lines used are readily available such that the technology can be transferred to a future turnkey protein manufacturer for clinical translation.

KEYWORDS
Chondrocytes, arthritis, osteoarthritis, lubricin, PRG4, lubrication

ACCOMPLISHMENTS

AIM 1: Designing and implementing a laboratory grade production of therapeutic lubricin candidates which can ultimately be replicated by a well-established turnkey partner for protein production who possess the capability to manufacture a large glycoprotein. **Rationale:** A potentially therapeutic lubricin must be identified, structurally defined and its mode of expression determined, which will directly impact its likelihood of manufacture.

Manufacture of Lubricin: Feasibility of Cell-based Manufacture

<table>
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<tr>
<th>Full Length 1</th>
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<td>Truncated 1029002</td>
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<td>Missing nucleotides 1381-2571</td>
<td>Truncated 1029003</td>
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<tr>
<td>4</td>
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<td>Truncated Preserving mid-mucin hinge 1029004</td>
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<td>Truncated Preserving mid-mucin hinge 1029005</td>
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<td>6</td>
<td>Missing 1381-1927 &amp; 2076-2571</td>
<td>Truncated Preserving mid-mucin hinge 1029006</td>
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We had succeeded in expressing all 5 of the shortened lubricin (PRG4) products as well as the full-length (PRG4) product. Digestion of the full-length product with NaNase I and O-glycosidase DS also confirmed that the post-translational glycosylations are O-linked β(1-3)GalNAc-Gal side chains. Upon digestion the molecular weight of the core was 151 kDa as predicted for the full-length PRG4 of 1404 amino acids. The yields from cell factories for each of the clones producing the 6 lubricins illustrated were 10 µg/ml in CHO-S cells. The defined bioprocess, which produced pre-GMP like material, was described in the last progress report and results in a highly purified product (Fig 1). It consists of all flow through steps utilizing anion exchange, hydroxyapatite and a hydrophobic exchange media resins.
Upon recloning into CHO-M cells (Selexis), which are a more suitable production platform for highly glycosylated proteins, we learned that much higher production levels could be achieved. The full-length and truncated constructs 4, 5 and 6 could all be expressed at levels of at least 1 mg/ml. This was very encouraging and rendered the rational selection of the rhPRG4 candidate being dependent on its lubricating ability. By contrast, constructs 2 and 3 continued to show low expression at the 10 µg/ml level. These two constructs were missing 3 glutamines in the central mucin domain that disrupted the repeating KEPAPTT sequence. We speculate these residues may be important in the hairpin twisting of the mucin domain and may disrupt the prolines which disallow secondary structure twisting.

The full-length rhPRG4 showed better lubricating ability of apposed explant pairs of 12 & 6 mm osteochondral discs in diameter harvested from the medial femoral condyle of bovine knees within 4 hours of slaughter (Fig 2). Attention was paid to the location in which explant pairs which were harvested from the mid region of the medial femoral condyle (see Results in Aim 2). Mechanical stimulation of apposing explant pairs was comprised of a 12N load of compression for 8 min, and 12 cycles of ± 720˚rotation. Static (COF\textsubscript{s}) and dynamic COF (COF\textsubscript{d}) were calculated from torque and axial load measured during the rotation sequence. COF\textsubscript{s} and COF\textsubscript{d} were calculated as follows:

\[
\text{COF}_s = \frac{T_{\text{max}}}{2/3 \times R \times F_{\text{eq}}};
\]

\[
\text{COF}_d = \frac{T_{\text{ave}}}{2/3 \times R \times F_{\text{eq}}}
\]

with \( T_{\text{max}} \) = torque max within the first 20˚ of rotation, \( T_{\text{ave}} \) = torque average for the last 720˚ of rotation, \( R \) = radius of the 6 mm explant, and \( F_{\text{eq}} \) = equilibrium force obtained after cartilage decompression.

**AIM 2:** Identify a candidate lubricin from Aim 1, which has maximal chondroprotection in an in vitro cartilage bearing model, which complements scalability, and a low cost-of-goods. **Rationale:**
Identification of a lubricin candidate, which is destined for GMP or GMP-like production, should demonstrate a reproducible in vitro ability to reduce COF and promote chondrocyte survival. We have previously shown that the chondrocytes in bovine osteochondral discs, which are loaded and oscillated, will display activated caspase-3 staining (a marker of chondrocyte apoptosis) when lubricated with an inadequate lubricant such as PBS. By contrast, these bearings lubricated by BSF, HSF or human synoviocyte lubricin show little or no caspase-3 staining. Elevated friction also caused these chondrocytes to become TUNEL positive. As pointed out in the last progress report, these procedures provide an experimental way to rationally confirm if the expressed rhPRG4 construct from Aim 1 is a therapeutic candidate relative to anticipated scalable costs. In addition, we have also cultured bovine osteochondral discs in the presence of IL-1α, an inflammatory cytokine, to ascertain if rhPRG4 can re-lubricate cartilage from an inflammatory environment. This is a critical in vitro test to determine if the chondroprotective device will work as intended in vivo.

We have concluded that the full-length rhPRG4 construct is the best candidate from both a chondroprotective and scalability vantage point. IL-1α stimulated explants lubricated with PBS (IL-1:PBS, n=17) displayed significantly higher COF compared to IL-1α stimulated, rhPRG4 lubricated explants (IL-1: rhPRG4, n=16) and rhPRG4 lubricated controls (Control:rhPRG4, n=19) for both COF$_a$ (**p<0.001, *p=0.01) and COF$_d$ (**p=0.002, *p=0.05), respectively (Fig 3). The significantly lower COF$_a$ (**p<0.001) and COF$_d$ (**p=0.002) for IL-1:rhPRG4 compared to IL-1:PBS explants indicated that rhPRG4 has the ability to restore normal lubricating ability to IL-1α treated explants. This is further supported qualitatively in Figure 4 where IL-1:rhPRG4 explants displayed a marked increase in PRG4 accumulation compared to IL-1α treated, non-mechanically stimulated, explanct controls. The increase in PRG4 accumulation for IL-1:rhPRG4 explants was significantly different than the nonexistent PRG4 accumulation seen in IL-1:PBS explants.

Explants from the anterior, mid, and posterior regions of the femoral condyle responded differently in terms of COF values upon mechanical testing. Explants in the anterior region with a known higher PRG4 concentration at the articular surface (based on prior work and that of Neu et al$^1$) displayed close to significant p values for COF$_a$ between IL-1:PBS and IL-1:rhPRG4 (p=0.09) as well as between IL-1:PBS and Control:PBS (p=0.07) but no significance for COF$_d$. Explants in the mid region displayed significance in COF$_a$ for IL-1:PBS and IL-1:rhPRG4 (**p=0.02) and close to significance in COF$_d$ for IL-1:PBS and IL-1:rhPRG4 (p=0.06). Explants in the posterior region with a known lower PRG4 concentration at the articular surface had no significant differences for COF$_a$ but COF$_d$ was significantly different for IL-1:PBS and IL-1:rhPRG4 (**p=0.005). These data, represented in Figure 5 below, suggest that the trend for rhPRG4 in restoring cartilage lubrication to IL-1α treated explants was conserved across these three areas of cartilage through reduction in either COF$_a$ or COF$_d$. However, the principal weight bearing area in the mid region of the condyle was most positively affected.

Furthermore, these data indicate that the anterior most cartilage may experience more lubricant effects from COF$_a$ reduction while cartilage in the posterior region may experience more lubricant effects from COF$_d$ under IL-1α exposure. Anterior explants appeared to be more impacted by IL-1α exposure alone for COF$_a$ compared to other articular cartilage regions. This idea was supported by 2-way ANOVA p-values looking at the effects of the lubricant alone (PBS vs rhPRG4), the test group alone (IL-1 vs. Control), and the interaction between these two experimental parameters for each region of cartilage. Anterior COF$_a$ indicated near significance between test groups alone (p= 0.07) while there is nothing close to significance for mid COF$_a$ (p=0.8) or posterior COF$_a$ (p= 0.27). In Fig 4 below, IL-1α treated controls displayed minimal or no PRG4 accumulation at the articular surface compared to media treated controls. The two aforementioned results may indicate that IL-1α exposure decreased the amount of PRG4 on the cartilage surface and that articular surfaces with increased PRG4 deposition at the surface were better able to protect articular cartilage from the effects of COF$_d$ compared to cartilage surfaces with less PRG4. Conversely cartilage surfaces in the posterior region with less surface lubricin may better protect against the effects of COF$_d$ vs COF$_a$. Whether or not this theory is true, the significantly higher COF$_a$ (**p=0.005) for IL-1:PBS compared to PBS-lubricated controls (Control:PBS, n=17), for cartilage regions overall, suggested that inflammation via IL-1α plays a role in increasing
COF\textsubscript{s} for cartilage-on-cartilage interactions. This study also indicates that native expression can be normalized by exogenous rhPRG4 (Fig 4, image row I, column B).

**Fig 3:** Static (right) and dynamic (left) coefficient of friction (COF) for IL-1\(\alpha\) treated (gray) and control (black) explants lubricated with either PBS (left) or rhPRG4 (right). IL-1:PBS treated explants displayed significantly higher COF compared to rhPRG4 lubricated explants for both COF\textsubscript{s} and COF\textsubscript{d}. Only COF\textsubscript{s} displayed significantly higher COF for IL-1:PBS over Control:PBS (p=0.005).

**Fig 4:** Immunohistological detection of PRG4 accumulation (green) in bovine explants. DAPI (blue) was used to stain cell nuclei. IL-1 treated controls (IL-1-Control: Row I: Column A&C) displayed decreased PRG4 accumulation compared to media treated explant controls (Media-Control: Row II: Column A&C). IL-1 treated explants mechanically tested with PBS (IL-1-PBS: Row I: Column D) displayed no change in PRG4 accumulation while IL-1 treated explants mechanically tested with rhPRG4 (IL-1:rhPRG4: Row I: Column B) displayed increased PRG4 accumulation comparable to Media-Control and media treated explants exposed to rhPRG4 without mechanical testing (Media-rhPRG4: Row II: Column A). White scale bar at the bottom right of each image is 40 \(\mu\)m. White arrows indicate PRG4 accumulation.
Thus, we have shown that full-length rhPRG4 is a potential therapeutic in the prevention of OA following joint trauma and in inflamed joints predisposed to OA based on other risk factors. The ability of this rhPRG4 to diminish activated caspase-3 in chondrocytes in these osteochondral explant bearings is presently being analyzed.

**Aim 3**: (To Begin Jan 2015). In this study we will utilize a large animal model to evaluate whether intra-articular injection of rhPRG4 following ACL transection will preserve cartilage after delayed ACL reconstruction (ACLR) surgery. **Rationale**: Large animal studies are a FDA required prelude to human studies. The porcine diarthrodial joint was selected as it is biomechanically more similar to human joints than those of other animal models.

**Timeline**

<table>
<thead>
<tr>
<th>Activities</th>
<th>FY</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
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<tr>
<td>Production of 5 truncated and full-length recombinant human lubricin in CHO-S cells</td>
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<tr>
<td>Study the 6 lubricin proteins in a cartilage bearing system to identify the one with the lowest cost and highest activity.</td>
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<td>Randomized and controlled trial of best candidate lubricin in a large animal model of PTOA induced by ACL transection.</td>
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Fig 5: Graphs of static (Row I) and dynamic (Row II) COF by cartilage region on the femoral condyle, anterior (Column A), mid (Column B), and posterior (Column C). Significance was found between IL-1:PBS (gray left) and IL-1:rhPRG4 (gray right) explant groups for mid COF (Row I: Column B: p=0.02) and posterior COF (Row II: Column C: p=0.005). Significance was close between IL-1:PBS and IL-1-rhPRG4 for anterior COF (Row I: Column A: p=0.09) and mid COF (Row II: Column B: p=0.06). The anterior most cartilage may experience more lubricant effects from COF reduction while cartilage in the posterior region may experience more lubricant effects from COF reduction under IL-1α exposure.
KEY RESEARCH ACCOMPLISHMENTS

- Rationalization that full-length rhPRG4 is a better lubricant than mucin domain truncated products
- Truncated products missing 3 glutamine residues in the center of the mucin domain significantly diminishes expression
- Expression of full-length rhPRG4 from CHO-M is possible and is a scalable production platform
- Full-length rhPRG4 as the selected construct for the large animal study in Aim 3 also reduced friction in IL-1 stimulated cartilage explants which partly recapitulates the environment of the post-traumatic joint

IMPACT

There is growing awareness that intra-articular hyaluronic acid injections are ineffective in chondroprotecting the traumatized joint. The American Academy of Orthopedic Surgeons no longer recommends viscosupplementation as a treatment for osteoarthritis. This void may be filled by tribosupplementation, using PRG4 which is the biopolymer that is fundamental in chondroprotective mechanisms. Given that PRG4 is down regulated in inflammation and trauma, efforts to utilize protein production platforms to manufacture rhPRG4 are a logical next step in preventing post traumatic osteoarthritis.

CHANGES/PROBLEMS

There have been no significant changes or delays in the conduct of this project. Preparation of rhPRG4 in Aim 2 did require an additional 2 months beyond our anticipated timeline. Thus Aim 3 will begin in January 2015 instead of the end of 2014 as originally proposed.

PRODUCTS

Publications


Invited Presentations


3. Jay, GD: 1st Annual McCaig Meeting on Osteoarthritis and Musculoskeletal Diseases, University of Calgary, Biomechanical Rationale of Tribosupplementation by Lubricin, Calgary, AL, Canada, May 2014. [Invited]

Abstracts


License

US Patent # 6,743,774 published in 2005 which describes PRG4 and its intended uses has been licensed by Rhode Island Hospital to Lubris, LLC (Framingham, MA). Lubris, LLC is a technology development start up focused on finding therapeutic uses for rhPRG4. A subsequent sublicense has recently been granted to Croma (Leobendorf, Austria) to further develop the tribosupplementation technology for traumatized joints in the prevention of post traumatic osteoarthritis.

CONCLUSIONS

Full-length rhPRG4 is the lubricant of choice in restoring chondroprotection to articular cartilage. This is also the case for inflamed cartilage which has been stimulated with IL-1. Histology for IL-1α treated explants displayed decreased PRG4 expression, which was rescued upon mechanical testing with rhPRG4 as a lubricant. Thus, rhPRG4 is a potential therapeutic in the prevention of OA following joint trauma and in inflamed joints predisposed to OA based on other risk factors. Full-length rhPRG4 will be tested in a large animal model in Aim 3 in the coming year.
## PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### Personnel

<table>
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<tr>
<th>Name</th>
<th>Project Role</th>
<th>Researcher Identifier (e.g. ORCID ID):</th>
<th>Nearest person month worked:</th>
<th>Contribution to Project:</th>
<th>Funding Support:</th>
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<td>Gregory Jay, MD, PhD</td>
<td>Principal Investigator</td>
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<td>Braden Fleming, PhD</td>
<td>Principal Investigator</td>
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<td>Ling Zhang, MD</td>
<td>Senior Research Assistant</td>
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<td>Kathryn Larson</td>
<td>Graduate Student</td>
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Research Support

Gregory Jay, MD, PhD

ACTIVE

P20 GM104937 (Chen) 9/10/12 - 8/31/17
NIH / NIGMS
COBRE for Skeletal Health and Repair
Bioengineering Core (Fleming) 1.2 calendar months

The goal of the Center of Biomedical Research Excellence (COBRE) is to establish a multi-disciplinary translational research center focusing on cartilage and joint health and disease mechanisms and developing repair strategy.
Role: Co-Mentor

PR110746 (Jay & Fleming) 9/30/12 – 9/29/15 2.4 calendar months
Department of Defense
Tribosupplementation with Lubricin in Prevention of Post-Traumatic Arthritis

The objective of this study is to determine if the intra-articular supplementation of recombinant “lubricin” will provide chondroprotection to the anterior cruciate ligament (ACL)-injured knee using a translational pre-clinical model.
Role: Principal Investigator

R42 AR057276 (Jay) 9/1/13-8/31/15 2.4 calendar months
NIH / NIAMS
Tribosupplementation of Injured Joints

Tribosupplementing mammalian joints with recombinant human lubricin can restore the protection of cartilage and prevent its damage. This practice following an injury, such as a meniscal tear or operative partial meniscectomy, may be pivotal in protecting a joint from developing degenerative joint disease. This animal study will show that injecting pre-commercialized lubricin protein into a joint can prevent joint degeneration.

PENDING

R01 AR067748 4/1/15 – 3/31/20 3.6 calendar months
NIH / NIAMS
Non-tribologic Bioactivity of Lubricin

The lubrication and protection of articular cartilage in joints is maintained by lubricin, a glycoprotein which coats cartilage and provides for lubrication in the absence of viscosity. The present application focuses on a novel non-lubricating role of lubricin and its interaction with CD44 which is inherently anti-inflammatory. By occupying this receptor on chondrocytes, lubricin may prevent catabolic metabolism in articular cartilage caused by pro-inflammatory cytokines, such as IL-1β which is elevated following in joint injury. Lubricin as a biologic may both lubricate cartilage surfaces and have a distinct and novel anti-inflammatory role.
Braden C. Fleming, PhD.

ACTIVE

PR110746 (Jay & Fleming) 9/30/12 – 9/29/15 2.4 calendar months
Department of Defense
Tribosupplementation with Lubricin in Prevention of Post-Traumatic Arthritis

The objective of this study is to determine if the intra-articular supplementation of recombinant “lubricin” will provide chondroprotection to the anterior cruciate ligament (ACL)-injured knee using a translational pre-clinical model.
Role: Principal Investigator

R01 AR047910 (Fleming) 8/1/09 – 7/31/14 1.8 calendar months
National Institutes of Health/NIAMS no cost extension
Effects of Initial Graft Tension on ACL Reconstruction

The effects of initial graft tension on surgical outcome following anterior cruciate ligament reconstruction are being evaluated in this prospective, randomized, controlled study using MR images to assess changes in cartilage volume, thickness, and structure.
Role: Principal Investigator.

R01 AR054099 (Murray) 6/1/10 – 5/31/15 1.2 calendar months
National Institutes of Health/NIAMS no cost extension
The Effect of Age on Functional ACL Healing

Optimizing the healing of adolescent ACL tissue so to match that seen in immature animals and to define the effect of delay on the efficacy of a surgical ACL repair.
Role: Co-Investigator (Site Principal Investigator)

R01 AR053684 (Spindler) 9/25/06 – 8/31/15 0.24 calendar months
National Institutes of Health/NIAMS
Prognosis and Predictors of ACL Reconstruction: A Multicenter Cohort Study

A multicenter prospective cohort study evaluating the prognosis and predictors of outcome following ACL reconstruction surgery.
Role: Co-Investigator

R01 AR056834 (Fleming/Murray) Renewal 2/1/09 – 8/31/18 1.8 calendar months
NIH
Bio-enhanced ACL Repair as a Modulator of Post-traumatic Osteoarthritis

The aims of this grant are to determine why a cartilage protection method, which we’ve develop to stop post-traumatic osteoarthritis after an ACL injury, works as well as translate it to the treatment of ACL injured patients. Another aim would be to extend the same cartilage protection to other traumatic joint injuries.
P20 GM104937 (Chen)  
National Institutes of Health  
COBRE for Skeletal Health and Repair – Bioengineering Core  
Program grant focusing on cartilage health.  
Role: Core B: Director/Project Mentor  

10/1/07 – 9/31/17  
0.9 calendar months

STTR/Tribologics (Jay)  
NIH  
Tribosupplementation for Injured Joints / Phase II  
Phase II is to prove the efficacy of tribosupplementation using a large animal pre-clinical model. We will also complete an evaluation of tribosupplementation following meniscal injury and/or partial meniscectomy since these injuries are much more common than ACL injuries and will extend the potential market base.  
Co-Investigator

9/1/13 – 8/31/15  
1.5 calendar months

R01 AR054099 (Crisco)  
National Institutes of Health  
Thumb CMC Biomechanics and Early OA Progression  
The major goal of this project is determine the relationships between joint biomechanics, gender and progression of early stage OA that will aid in the development of new treatment options and in the design of better surgical procedures

06/01/11 – 3/31/16  
0.26 calendar months

R01 AR065462 (Fleming/Murray)  
NIH/NIAMS  
Non-invasive Assessment of Ligament Healing in Vivo  
The objective of this study is to use magnetic resonance imaging (MRI) technique to accurately predict the biomechanical properties of a healing ligament without harming any tissue.

PENDING

Dept. of Defense (Murray/Fleming)  
6/1/15 – 5/31/18  
1.2 calendar months

Novel Therapeutic for Post-traumatic Osteoarthritis (OA)  
The aims of this grant are to further demonstrate the effectiveness of a novel therapeutic scaffold treatment method, and to translate this technology to patients at risk for post-traumatic osteoarthritis. An added benefit of this approach is that it can be implemented in the field.

OVERLAP

The is no overlap at this time.
What other organizations were involved as partners?

Organization Name: Boston Children’s Hospital
Location of Organization: Boston, MA
Partner's contribution: At Boston Children’s Hospital, Dr. Martha Murray has assisted in the preparations to initiate Aim 3 and she will be the principal surgeon overseeing the ACL transections and reconstructions.
Financial support: A subcontract was executed between Rhode Island Hospital and Boston Children’s Hospital, as outlined in the original application, to support the contribution of Dr. Murray.
In-kind support: N/A
Facilities: Dr. Murray and her staff have visited the Brown University Vivarium where the large animal trial will be conducted in Aim 3.
Collaboration: (e.g., partner's staff work with project staff on the project);
Personnel exchanges: Dr. Murray and her staff have visited the Brown University Vivarium where the large animal trial will be conducted in Aim 3.
Other:

REFERENCES