Mechanistic Ancillary Studies to Ongoing Interventional Clinical Trials (R01 and R21) Review: RFA-AR-19-006 and RFA-AR-19-007

Application #: AR19-006

Principal Investigator(s): Beynnon, Bruce

OVERALL IMPACT

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact.

Overall Impact: *Write a paragraph summarizing the factors that informed your Overall Impact score.*
In this proposal, a highly experienced and talented research team will address a critical barrier to understanding how adaptive responses in bone, cartilage and muscle following traumatic ACL injury impact the development PTOA- a common outcome following ACL repair. To address this complex problem, the investigators propose an ancillary prospective study that will dovetail well with their recently funded RO1 proposal that examines risk factors for contralateral ACL injury. They will enroll 120 patients in the parent study and it is estimated that around 22% will experience a contralateral ACR injury within 2 years. They are collecting a detailed MRI and functional data at baseline of both the involved and uninvolved knee that they will be able to evaluate in those patients who suffer a 2nd injury within the allotted timeframe. They are including novel MRI imaging assessments of bone quality and an approach that more effectively mimics biomechanical stress during the collection of MRI images. Key variables such as sex and type of trauma will be examined and the effects on skeletal muscle size and function, bone architecture and articular cartilage matrix components examined. Minor weakness include not mentioning how surgical technique may alter outcomes, the fact that risk factors for the initial ACL and subsequent contralateral ACL injury may be different and a rather aggressive recruitment timeline that while challenging, is feasible. Of course the feasibility will also be impacted by the % of athletes that develop a contralateral injury in the defined window. Overall, this is an extremely strong proposal with possibility for high impact in the field.

SCORED REVIEW CRITERIA

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance: Does the project address an important problem or a critical barrier to progress in the field? Is there a strong scientific premise for the project? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field? *Specific to this FOA:* What is the significance of the new mechanistic insight to be gained from the proposed study? Does the proposed ancillary study enhance the scientific content and value of the parent project(s)?
Strengths

- The critical barriers regarding the prevention and treatment of PTOA after symptomatic injury are identified and addressing them is a major priority especially since it typically involves young athletes.
- The premise is based on the concept that understanding adaptive responses of the limb to the injury in the bone, cartilage and muscle will help to identify early informative biomarkers to facilitate early intervention.
- Successful completion of the aims will aid in the understanding of the progression of joint pathology after injury by examining cartilage thickness, an early marker of PTOA and potentially reveal novel biomarkers and to inform new treatment approaches
- Through the introduction of a prospective study design, the investigators have great potential to identify key factors that place patients at a risk for a second injury and this element greatly enhances the scientific content of the parent study.

Weaknesses

- This study will provide information regarding the risk factors for contralateral ACL injury but it is not entirely clear whether these data will strongly reflect risk factors for the initial event since post-surgical tissue adaptation may uncover new variables that increase the risk of a second injury. This is a minor drawback.

2. Investigator(s): Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Specific to this FOA: Does the application describe how the PD(s)/PI(s) of the ancillary study and the parent project interact on a regular basis and work cooperatively to ensure the successful completion of the ancillary study while maintaining the integrity of the parent project?

Strengths

- The investigative team is in experienced in the field of AC-related trauma, they have a long record of NIH funding coupled with high impact publications and they have worked closely in a collaborative manner for a long period of time.

Weaknesses

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3. Innovation: Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Strengths

- The proposed ancillary studies include a prospective study of the adaptive response to severe trauma in the contralateral limb by including patients in the parent study in a novel trial design.
- They are examining key unexplored variables including sex and combined data from contact and non-contact injuries
- Inclusion of a brace during the MRI that reproduces loading conditions that stress articular cartilage and meniscus that will more closely align with the biomechanical stress encountered by athletes in the field.

Weaknesses

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4. Approach: Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects? If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of children, justified in terms of the scientific goals and research strategy proposed?

Specific to this FOA: From the description of the parent study synopsis: does the parent project provide sufficient well-characterized patients, biological samples and/or clinical data for the ancillary study?

Strengths

- The creation of a prospective study design in the ancillary study greatly enhances the type of information that can be obtained from the parent study and is feasible since imaging and assessments of overall function are obtained at baseline
- The methodology and analytic approaches are well delineated and feasible and the MRI-based assessment of bone architecture and application of biomechanical stress during imaging will provide new information regarding bone and cartilage response to trauma.
- Biologic variables such as sex and type of trauma included in the analyses.

Weaknesses

- Surgical technique and the type of repair can greatly influence outcomes but this is not discussed
- The factors that increase risk for a contralateral injury may differ from those that were related to the initial injury due to the altered post-surgical mechanics. This difference is not discussed but this is a minor issue.
- The recruitment time line is aggressive but the team has a large and collaborative high school network making the ancillary study feasible.

- If significantly less than 22% of athletes develop a contralateral injury, the study will be underpowered.
- Potential pitfalls and alternative strategies are not discussed but given the experience and track record of the team, I don't think this is a major weakness.

5. Environment: Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Strengths

- The University of Vermont and State Agricultural College are an outstanding environment for this ancillary and parent study. They investigators have support from the institution along with collaborations with over 17 area high schools who refer injured athletes for ACL repair. The PhD investigators have well equipped laboratories and Dr. Slauterback and 2 colleagues perform the ACR repair.

Weaknesses

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ADDITIONAL REVIEW CRITERIA

As applicable for the project proposed, reviewers will consider the following additional items in the determination of scientific and technical merit, but will not give separate scores for these items**.**

— Responses for Protections for Human Subjects, Vertebrate Animals, and Biohazards **are required from reviewers for all applications**.

— A response for Inclusion Plans is required from reviewers for applications proposing Human Subjects Research, except those designated Exemption 4.

Time Sensitivity Justification: **The committee will evaluate the adequacy of the justification for time-sensitivity of the proposed project.**

Comments (Required):

- This is time sensitive since subjects must be recruited in the first 2 years so they can be followed for 2 years following the surgical repair on the contralateral limb.

Protections for Human Subjects

Click Here to Select

Comments (Required Unless Not Applicable):

- These have been adequately addressed

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

Comments (Required Unless Not Applicable):

-

Inclusion Plans: **Applicable Only for Human Subjects research and not IRB Exemption #4.**

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion Based on Age: Distribution justified scientifically

Comments (Required Unless Not Applicable):

- They have addressed age sex and ethnicity

Vertebrate Animals

Is the proposed research involving vertebrate animals scientifically appropriate, including the justifications for animal usage and protections for research animals described in the Vertebrate Animals section (and method of euthanasia described in the Cover Page Supplement or PHS Supplemental Form, if applicable)?

Not Applicable (No Vertebrate Animals)

Comments (Required Unless Not Applicable):

-

Biohazards

Click Here to Select

Comments (Required Unless Not Applicable):

- Not applicable

Resubmission

Comments (if applicable):

-

Revision

Comments (if applicable):

-

ADDITIONAL REVIEW CONSIDERATIONS

As applicable for the project proposed, reviewers will address each of the following items, but will not give scores for these items and should not consider them in providing an overall impact/priority score.

Select Agents
Acceptable Comments (Required if Unacceptable): •

Resource Sharing Plans
Acceptable Comments (Required if Unacceptable): •

Authentication of Key Biological and/or Chemical Resources
Acceptable Comments (Required if Unacceptable): •

Budget and Period of Support
Recommend as Requested Recommended budget modifications or possible overlap identified: • Overlap not indentified