UNIVERSITY OF OREGON

Consent for Research Participation

Title: **Myosin Binding Protein C Mediates Age-Related Skeletal Fatigability**

Sponsor: This study is funded by The Wu Tsai Human Performance Alliance, the NIH (R21AG077125-01A) and start-up funds provided to Dr. Callahan by the University of Oregon.

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and colleagues

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You are being asked to participate in a research study. Your participation is voluntary and you are free to withdraw participation at any time, for any reason. The box below highlights key information about this research for you to consider when making a decision whether or not to participate. Carefully consider this information and the more detailed information provided below the box. Please ask questions about any of the information you do not understand before you decide whether to participate.

Key Information for You to Consider

- **Voluntary Consent**. You are being asked to volunteer for a research study. It is up to you whether you choose to participate or not. There will be no penalty or loss of benefits to which you are otherwise entitled if you choose not to participate or discontinue participation.
- **Purpose**. The purpose of this research is to better understand how age and fatigue affect muscle structure and function. We will test the idea that specific proteins within the muscle explain age and fatigue-related changes to muscle performance.
- **Duration.** It is expected that your participation will last a total of 3 hours between 3 visits to the lab.
- **Procedures and Activities.** If you agree to be in this study, study coordinators will ask you about your medical history, what medications you are currently taking and ask you to complete questionnaires asking about your health and physical activity.

  At your screening appointment (the first of three appointments in this study) we will meet in the muscle cellular biology lab to review this document and address any questions you might have about participating. Before conclusion of this visit, you will also be provided with a physical activity monitor, a small electronic device about the size of a credit card. We will ask you to wear this monitor affixed with adhesive to the front of your thigh for the 5-10 days separating your first and second visits to the lab. The monitor will record how much you move your body (not where or how) and help us characterize differences in physical activity between volunteers. Lastly, we will measure the strength of the muscles used to straighten your leg in your dominant leg. You will be asked to perform repeated voluntary contractions of these muscles until they are fatigued. Before and after these contractions, ultrasound images and measures of muscle stiffness will be acquired at two locations on your leg, one on the side of your thigh and the other just below your kneecap. The total time for this visit is approximately 40 minutes.

Approximately one week following the screening visit, you will be asked to visit the lab a second time, where you will be asked to perform repeated voluntary contractions of the muscles used to straighten your leg in one leg until the muscle becomes fatigued. Immediately following exercise we will perform a biopsy on the muscle of the fatigued leg. After the first biopsy is completed, a second biopsy will be performed on the corresponding muscle of the opposite leg. This visit will last approximately 2 hours.
A 3rd, optional visit, will take place 5-7 days following visit 2 to inspect the biopsy incision and receive study payment. This visit will last approximately 15 minutes.

- **Risks.** Risks from exercise include feeling out of breath and/or some soreness in the exercised muscle in the days following the study. This discomfort is usually described as moderate and subsides within 24-48 hours. Potential risk from electromyography include skin irritation from adhesives used to affix electrodes. The potential risks of the biopsy procedure are some pain, bleeding, bruising, infection, numbness and scar at the site of biopsy.
- **Benefits**. You will likely receive no direct benefit from your participation in this study but the methods we develop and the information we obtain will help us to expand the ability of the lab to better understand muscle physiology.
- **Alternatives.** This research is being conducted to gather information. Participation is voluntary and the only alternative is to not participate.

Who is conducting this research?

The researchers Damien Callahan, Hans Dreyer, and Craig Davidson from the University of Oregon along with Larry David from Oregon Health and Science University and Bertrand Tanner from Washington State University are asking for your consent to this research. The researchers have declared no conflicts of interest related to this study.

How long will I be in this research?

We expect that your participation will last a between 3 hours and 2 hours and 45 minutes (45 minutes for the first visit, 2 hours for the second, and 15 minutes for the optional 3rd visit). A brief (about 15 min) 3rd visit is **optional** to confirm proper healing of the biopsy sites and remove the stitch if one was used to close the sites of your muscle biopsies. **If you do not have a stitch and would rather avoid this visit, you may email an electronic photograph of the biopsy site to research personnel who will confirm proper healing of the biopsy site.** Timeline and events in the 3 study visits is provided below.

Timeline (min)	0 - 15	16 - 30	31 - 45	46 - 60	61 - 75	76 - 90	91 - 105	106 - 120
Day 1	Informed Consent Review & Physical Activity Monitor	Muscle stiffness measures and fatiguing exercise (dominant limb)						
5 - 10 days interim								
Day 2	Orientation/Review protocol	EMG prep & Peak power testing + recovery		Fatiguing exercise (dominant limb)	Muscle biopsy from exercised limb		Muscle biopsy from non-exercised limb	
5 - 7 days interim								
Day 3	Biopsy site inspection followup							

All research personnel and volunteers will be asked to wear masks during all study visits.

What happens if I agree to participate in this research?

If you agree to be in this study, study coordinators will ask you about your medical history, what medications you are currently taking and ask you to complete questionnaires asking about your health and physical activity. This would take place at your screening appointment.

At your screening appointment (the first of three appointments in this study) you will meet with 1 research personnel at the Muscle Cellular Biology Laboratory to review this consent document and perform a preliminary set of data collection. You will be asked to perform repeated voluntary contractions of the muscles used to straighten your leg until the muscle becomes fatigued. Before and after this exercise, we will measure the stiffness of muscles and tendons under your skin using ultrasound imaging and a small mechanical probe (MyotonPro, described below). For ultrasound imaging, a clear gel will be applied to the transducer to maintain quality of the ultrasound image. Ultrasound imaging will take place on the lateral thigh and on the front of your knee, just below the knee cap (patellar tendon). At the patellar tendon, a piece of 2mm wide surgical tape will be placed across the skin over the midline of the patellar tendon to create visible markers for measurement. The probe will be fixed to the respective location by a custom mounting device. Upon placement of the ultrasound probe of the thigh, three images will be captured for muscle composition analysis. For musculoskeletal stiffness measures, a MyotonPro device will be used. This application is consistent with manufacturer instructions, but is not approved or cleared with the Food and Drug Administration (FDA). Therefore, use of the MyotonPro is experimental. To measure how stiff your muscles at this site are, the device pushes down with about the pressure required to click a pen (0.2N). At the thigh, the MyotonPro will record stiffness adjacent to the ultrasound probe. The MyotonPro and ultrasound probes will be held in place with a custom-built brace that will be wrapped around your thigh with moderate pressure (similar to a form-fitting garment). At the patellar tendon, an experimenter will hold the device perpendicular to the knee, while maintaining tissue contact. All measurements will occur contemporaneously with each contraction. For the bout of maximum voluntary contractions and initial set of repeated submaximal contractions, ultrasound imaging and MyotonPro stiffness measurements will occur at the thigh. During the second set of contractions, ultrasound imaging will take place at the patellar tendon. Before conclusion of this visit, you will be provided with a physical activity monitor, a small electronic device about the size of a credit card. We will ask you to wear this monitor affixed with adhesive cover to the front of your thigh for the 5-10 days separating your first and second visits to the lab. The monitor will record how much you move your body (not where or how) and help us characterize differences in physical activity between volunteers. To improve adherence of the adhesive, it may be helpful to shave, and cleanse with alcohol swab, a portion of your thigh where the monitor is affixed. This can be determined during Study Day 1 **and performed by Dr. Callahan or yourself**.

Approximately one week following the screening visit, you will be asked to visit the lab for a second visit. Please come to this visit hydrated (i.e., drink a glass of water prior to your arrival), but fasted, having nothing to eat the day of this visit prior to coming in. During this visit, you will be asked to perform repeated voluntary contractions of the muscles used to straighten your leg in one leg until the muscle becomes fatigued. During this fatiguing bout of exercise, we will record the naturally occurring electrical activity of the exercising muscles using electromyography (EMG). Small (1x2 cm) electrodes will be placed on the front of your thigh before the exercise begins. Prior to placement, the skin in this location will be prepared by cleansing with an alcohol swab, gentle abrasion and shaving if necessary. The electrodes will be prepared with conducting gel and affixed to the leg using strips of micropore tape. These electrodes will be removed at the conclusion of fatiguing exercise.

Immediately following exercise to fatigue one leg, you will be asked to transition to a nearby bed for the biopsy procedures. During the procedure, you will be asked to lay down on your back on this bed with the leg to be biopsied exposed (wearing shorts is encouraged). Thereafter, a muscle biopsy will be performed on the muscles of the fatigued leg. After the first biopsy is completed, a second biopsy will be performed on the corresponding muscle of the opposite limb. The muscle biopsy procedure will be performed using sterile technique, meaning the skin of your legs near the sites of the biopsies will be cleansed with antiseptic solution and anything touching your limb following that point will be sterile. Biopsies will be obtained of a large muscle at the side of your thigh (vastus lateralis) using standard techniques (sterile procedure and local anesthesia, lidocaine) by a trained member of the research team.

This procedure involves taking a small piece of tissue from your leg. The total size of this tissue will be approximately 100mg, or the size of a black bean. The skin is cleaned and made sterile, and the skin and tissue below are injected with local anesthetic (numbing medicine) to minimize pain. We will make a small incision about 1cm, or the size of this dash "_____" at mid-thigh, through which a needle with a diameter about the size

of this letter "**O**" will be advanced into the muscle. A piece of tissue will then be removed. It is possible all necessary tissue will be extracted in the first insertion and tissue removal (a "pass"), but it is reasonable to expect that two or more passes will be required to obtain sufficient tissue. We will ask your permission to continue if we need to make additional passes. No more than 5 passes will be attempted. The incision will be closed with adhesive bandages and additional adhesive solution (benzoin tincture) and/or a single stich. The total length of time for each of the two biopsies will be approximately thirty (30) to forty-five (45) minutes. Combined with the single-leg exercise, the total length of time for the second visit will be approximately 2 hours.

Special Note

Please do not take NSAIDs (Aspirin, Advil, Motrin, Aleve, for example) for at least 4 days leading up to the biopsy (Acetaminophen is ok). You may take NSAIDs after the biopsy, as needed. Further, questions related to diabetes and alcohol consumption serve the dual purpose of describing our study population and screening individuals from participation that might have elevated risk of bleeding and delayed wound healing following the muscle biopsy. Participants that have diabetes or consume excessive amounts of alcohol may experience delayed wound healing. Participants should not consume excessive amounts of alcohol because it is important for healing. Please consider these factors and answer these questions as fully and honestly as possible.

Follow-up

You will be contacted about 24 hours after the biopsy to report on condition of the biopsy sites. The follow-up will take less than 5 minutes. This is to monitor for infection and proper incision closure. You will also be asked to return 5-7 days following the biopsy so the stitches may be safely removed (if they were placed) and incision inspected for signs of infection. **This visit is optional and may be substituted by sending a picture of the biopsy site to research personnel via email.**

What happens to the information collected for this research?

Information and/or specimens collected for this research will be used to establish links between specific proteins in your muscle and how those muscles contract as well as how those links are affected by intracellular metabolism. We are also interested in whether a person's age affects these relationships. It is anticipated this information will contribute to proposals for funding that might support larger-scale investigations. If publishable data are generated from this study, your name will not be used in any reports or presentations of study results. Data and biospecimens shared between members of the research team for purposes of analysis will be coded and deidentified.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

In the event biospecimens are used for future research or distributed to another investigator for future research, any and all identifiers will be removed from biospecimen ID or associated information. Use of biospecimens for future research may be done without obtaining additional consent.

How will my privacy and data confidentiality be protected?

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission. Participant identities will be kept confidential by assigning you a "participant identification number". The names associated with each participant identification number will be kept in a locked file cabinet in Dr. Callahan's office area.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be

used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the National Institute on Aging which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.UO Research Compliance Services may need to review records of individual participants. As a result, they may see your name, but they are bound by rules of confidentiality not to reveal your identity to others. The researchers may store coded data gathered during this study indefinitely.

Because this study involves use of a measurement device (MyotonPro) not approved by the Food and Drug Administration (FDA), we will comply with FDA requirements consistent with non-significant risk determinations for the device. It is possible that the FDA may inspect study records. The data collected on study volunteers to the point of withdrawal/completion will remain part of the study database and may not be removed in order to comply with FDA requirements.

The research team includes individuals who are mandatory reporters. If the research team has reasonable cause to suspect abuse or neglect of a child or adult, a report may be required under Oregon State Law. In such a case, the research team may be obligated to breach confidentiality and may be required to disclose personal information.

What are the risks if I participate in this research?
Activity Monitor: Some discomfort is a potential risk associated with wearing the physical activity monitor for 5 – 10 days. Further, you may be exposed to potentially irritating adhesives, like those used for EMG (below). If you experience irritation in response to adhesives used to secure the monitor, we will use alternate means of fixation including physio tape, athletic wrap, etc. instead of adhesive tape.

Electromyography (EMG): Risks related to EMG are related to skin preparation and use of adhesive to affix the surface electrodes; namely some scuffing or scabs may result from skin abrasion and adhesives may cause skin irritation.

Fatiguing Exercise: Risks from exercise include feeling out of breath and/or some soreness in the exercised muscle in the days following the study. This discomfort is usually described as moderate and subsides within 24-48 hours.

Muscle Stiffness Measures: There is no risk associated with ultrasonography directly, but volunteers may experience some irritation from adhesives used in the surgical tape placed on the patellar tendon. Volunteers may also experience irritation from water-soluble gel application at the designated locations, which is necessary for acoustic coupling. Irritation in response to either of these topical exposures is very rare. Following our measures, the sites will be thoroughly cleansed with warm soapy water to minimize the time volunteers are exposed to potentially irritating substances.

Muscle Biopsy: The potential risks of the biopsy procedure are some pain, bleeding, bruising, infection, and scar at the site of biopsy. Careful sterile technique should reduce the likelihood of any of these complications. The risk of bleeding from the biopsy site is 2 in 1000; the risk of bruising or blue-and-black mark is 14 in 1000; and the

risk of infection is so small that the precise number is unknown. Additionally, you may experience numbness around the area of the biopsy site (approximately 2x2 inches in area), which will likely go away with time (sensation returns) but in very rare instances sensation may never return. The risk that you experience numbness is less than 5 in 1000 and the risk that the numbness never goes away is much less. The risk of pain during the biopsy is very small since local numbing medication (lidocaine) will be used during the biopsies to remove or minimize sensation, but some individuals will experience brief (a few seconds) sensations of pressure or pulling during the biopsy. After a biopsy you have a 5 in 10 chance of experiencing soreness at the site of biopsy for 24 to 48 hours. These risks are slightly increased with each additional pass during the biopsy. Over the counter medication will be enough to minimize any potential pain from the biopsy site. The scar will be approximately 1cm long like this dash "_____". Also, you will likely experience some discomfort (burning sensation) from the numbing medication. The other risks associated with local anesthetics include nervousness, dizziness, blurred vision, tremor, drowsiness, tinnitus, numbness, disorientation, hypotension, nausea and vomiting. However, the risk of these adverse reactions occurring is very low. If you have ever had an allergic reaction to lidocaine we will not allow you participate. We will close the biopsy incision using surgical adhesive tape with additional adhesive solution that will reinforce the surgical tape (Benzoin). Benzoin is used to improve the adhesion of surgical tapes and enhance skin integrity at the site of closure. However, some people have experienced sensitivity to adhesives and/or topical benzoin. If you experience a rash or inflammation from the tape or the benzoin, the tape and/or benzoin will be removed and we will use a single stitch to close the incision. Finally, some volunteers might faint at the sight of blood or a needle (vasovagal syncope) as at a blood draw. This is rare (less than 5 in 100), but if it occurs, you will remain reclined in the subject bed to promote and restore blood flow to your head. At the University of Oregon, we have performed muscle biopsies on over 400 adults without incident.

Updates to Risk Assessment: Any new findings that develop during the course of your participation that might relate to your willingness to continue participation will be shared with you.

What are the benefits of participating in this research?

You will likely receive no direct benefit from your participation in this study but the methods we develop and the information we obtain will help us to expand the ability of the lab to better understand muscle physiology.

What other choices do I have besides participation in this research?

This research is being conducted to gather information. You are free to choose not to take part in this study.

What if I want to stop participating in this research?

Taking part in this research study is your decision. Your participation in this study is voluntary. You do not have to take part in this study, but if you do, you can stop at any time. You have the right to choose not to participate in any study activity or completely withdraw from continued participation at any point in this study without penalty or loss of benefits to which you are otherwise entitled. Your decision whether or not to participate will not affect your relationship with the researchers or the University of Oregon.

Can I be withdrawn from participation?

Under the following circumstances, to maintain appropriate safety and research integrity standards, you may be withdrawn from participation. Reasons for withdrawal might include, but are not limited to:

a. It is in your best interest
b. You have a side effect that requires stopping the research
c. You need a treatment not allowed in this research
d. You experience orthopedic injury unrelated to study activities but that limit your ability to perform knee extension exercise or receive a muscle biopsy

e. The research is canceled by the FDA, the sponsor or the IRB
g. You are unable to comply with study protocols

In the event you are withdrawn from participation, renumeration will follow the prorated schedule listed below in the section titled "**Will I be paid for participating in this research?**"

Will it cost me money to take part in this research?

There are no costs associated with participating in this research study.

What if I am injured because of participating in this research?

If you are injured or get sick because of being in this research, seek medical care and call the researchers immediately.

In the event you suffer a research -related injury your medical expenses will be your responsibility or that of your insurance company (or other third-party payer), although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research. If you are a UO student or employee and are covered by a UO medical plan, that plan might have terms that apply to your injury.

If you experience harm because of the project, you can ask the State of Oregon to pay you. If you have been harmed, there are two University representatives you need to contact. Here are their addresses and phone numbers:

General Counsel/ Office of the President
1226 University of Oregon
Eugene, OR 97403-1226
(541) 346-3082

Research Compliance Services
5237 University of Oregon
Eugene, OR 97403-5237
(541) 346-2510

A law called the Oregon Tort Claims Act may limit the amount of money you can receive from the State of Oregon if you are harmed.

Will I be paid for participating in this research?

For taking part in this research, you may be paid up to a total of $**200**. Your compensation will be broken down as follows:

Day 1 (Consent and muscle testing): $20

Day 2 (collect PA monitor): $10 ($30 total)

Day 2 (Fatiguing Exercise and post-fatigue biopsy): $100 ($130 total)

Day 2 (Non-Fatigued Biopsy): $70 ($200 total)

Should a participant not reach one of the defined compensation endpoints above, the amount of compensation will revert back to the last complete interval (no pro-rating between study intervals). For example, a participant who completes the exercise and first biopsy on study day 2, but withdraws from the study prior to second biopsy would be eligible to receive $130.00 compensation. In the case of muscle biopsies, the interval is considered complete if an incision is made, i.e., we need not obtain a usable sample for you to be compensated. There is absolutely no chance that your specimens could ever be used for commercial profit.

Please be aware, compensation for participation in research may be considered taxable income. The University requires tracking for compensation that is paid to you; this may include your name and contact information. This information is stored confidentially and separate from research data. If you receive $600 or more in a calendar

year, you may be contacted to provide additional information (e.g. Social Security Number) for tax reporting purposes.

Who can answer my questions about this research?

If you have questions, concerns, or have experienced a research related injury, contact the research team at:

Damien Callahan
541-346-5040
damienc@uoregon.edu
or
uo.mcbl@gmail.com

An Institutional Review Board ("IRB") is overseeing this research. An IRB is a group of people who perform independent review of research studies to ensure the rights and welfare of participants are protected. UO Research Compliance Services is the office that supports the IRB. If you have questions about your rights or wish to speak with someone other than the research team, you may contact:

Research Compliance Services
5237 University of Oregon
Eugene, OR 97403-5237
(541) 346-2510
researchcompliance@uoregon.edu

STATEMENT OF CONSENT

I have had the opportunity to read and consider the information in this form. I have asked any questions necessary to make a decision about my participation. I understand that I can ask additional questions throughout my participation.

I understand that by signing below, I volunteer to participate in this research. I understand that I am not waiving any legal rights. I have been provided with a copy of this consent form. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

I consent to participate in this study.

Name of Adult Participant	Signature of Adult Participant	Date

Researcher Signature (to be completed at time of informed consent)

I have explained the research to the participant and answered all of his/her questions. I believe that he/she understands the information described in this consent form and freely consents to participate.

Name of Research Team Member	Signature of Research Team Member	Date