## Interdisciplinary Research (IDR) Origination Awards

Cover Page

#### **Project Title**

Title: Using imaging to understand Achilles tendon adaptation and injury in female athletes

#### **Principal Investigator(s)**

Name (PI listed first)	Department	College
Wayne Johnson	Exercise Sciences	Life Sciences
Steven Allen	Electrical and Computer Engineering	Engineering
Shayla Bott	Dance	Fine Arts and Communications
Christopher Dillon	Mechanical Engineering	Engineering

#### Track

Track One

#### Abstract

Female adults suffer high rates of Achilles tendon injury that cause pain or tendon rupture and significantly affect quality of life. Following Achilles tendon injury, females have more complications while experiencing less benefit from current therapeutic interventions when compared with male counterparts. Despite high rates and significant consequences of Achilles tendon injury in females, there is a lack of knowledge about how the intensity and duration of activity induces beneficial or adverse adaptations in female Achilles tendons. For example, it is unknown how estrogen and progesterone, which can limit collagen synthesis, may possibly influence tendon health and growth. This knowledge gap contributes to an inability, among healthcare professionals, to appropriately predict and optimally treat Achilles tendon injuries in female athletes.

Here, we propose a series of experiments using novel imaging methods to identify characteristics of female Achilles tendon injury in an understudied population of female dancers and to discriminate between healthy and injurious Achilles tendon tissue remodeling. These experiments will account for the potential effects of the menstrual cycle. Further our study hypothesizes that healthy and adverse tendon remodeling (where tendon collagen reorganizes in an attempt to prepare for future activity) closely correlates with exercise-induced transfer of water, nutrients, and signaling factors through the tendon. Such transfer will be characterized with novel imaging methods. It further hypothesizes that measures of water content and fluid transfer in the Achilles tendon as females undergo various intensities of exercise will differentiate between beneficial and adverse remodeling.

#### **Summary of Plans for External Funding**

Our assembled team will aim to submit four external grant proposals during the award period. All of these grants will use the results from these studies as preliminary data for submission. Three minor grants (<\$100,000) and one major grant (>\$100,000) will be applied for. The minor grants include: 1) The Research Endowment Award sponsored by the American College of Sports Medicine, awarded for research that pertains to clinical sports medicine. 2) The Academy of Orthopedic Physical Therapy Established Research Program for research in an area examining treatment programs. 3) The American Orthopedic Foot and Ankle Society grants projects for research in the foot and ankle area. In order to apply for each of these grants one member on the grant must be an affiliated member of the institution. A. Wayne Johnson has membership affiliation with each of these organizations. Near the end of the study, we will use our study results as preliminary data for an R01 award sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Disease.

#### **Project Narrative**

#### I. Introduction

Female adults and athletes suffer high rates of Achilles tendon injuries that cause severe pain or tendon rupture [2, 3]. Without prevention or effective therapy, these injuries impede or even end participation in exercise at a time where maintained activity strongly affects health in later years [4, 5]. Furthermore, after injury, females tend to suffer more relative to their male counterparts [4, 6], and benefit less from therapeutic treatments [7]. For example, after Achilles injury, females sit-out from exercise over more days [8], more frequently require surgery, and suffer nearly double the reinjury rate relative to men that participate in similarly intense levels of exercise [8]. Finally, female dominant sports, such as gymnastics and dance, suffer very high rates of Achilles injury when compared with other sports [8, 9]. These high injury rates ensure that many women engaged in these forms of exercise experience pain or injury and thereby suffer a reduced quality of life which may persist into the future.

The disparity in tendon health between men and women is exacerbated by a void of understanding about how the female tendon responds to increases in activity and loading [10] despite equal prevalence of injury [2]. For example, while tendon remodeling processes in females are thought to change with progesterone and estrogen levels inherent to the menstrual cycle, it is unknown what these changes entirely entail [11]. In fact, some studies in tendon health exclude females [12], leading to therapies optimized for men but with lower efficacy for women [7]. The lack of knowledge about female tendon adaptations contributes to a void of understanding about why some exercise instances harm tendons while others do not [11]. The result is training and sporting regimens that don't prevent injury [4], therapies that ineffectively resolve injury [7], and an inability to identify when a person's tendon is at risk of injury.

Here, we propose a series of controlled experiments using novel imaging tools not commonly employed by athletic trainers and medical staff to identify female Achilles tendon features that discriminate between healthy and injurious responses to activity. These experiments are deliberately designed to account for the potential effects of the menstrual cycle. More specifically, this study hypothesizes that healthy and adverse tendon remodeling (where tendon collagen reorganizes in an attempt to prepare for future activity) closely correlates with the manner by which exercise transfers water, nutrients, and signaling factors, as characterized by imaging, through the tendon. It further hypothesizes that measures of water content and transfer in the Achilles tendon as females undergo exercise will differentiate between beneficial and adverse remodeling activity.

The results of this study will help athletes, medical professionals, and future researchers better identify and protect female tendons on the verge of injury. They will produce a catalogue of features that discriminate when tendons are undergoing a beneficial remodeling process and when they are undergoing an adverse remodeling process. These results will inform the formation of training regimens and therapeutic strategies that better cater to the unique physiology of female athletes. In particular, this study will benefit the large proportion of female athletes in dance, gymnastics, and other female-dominant sports who suffer Achilles injury at high rates.

#### **II.** Achilles tendon adaptations

The Achilles Tendon has almost ideal mechanical properties for transmitting force produced by the gastrocnemius and soleus muscles to the calcaneus bone thereby causing movement [13, 14]. Despite the ideal properties of the Achilles tendon, it is one of the most frequently injured tendons in the body [15], with the highest rate of tendon rupture [16].

During movement, the Achilles tendon experiences tremendous loading forces [17] that can cause short-term and long-term adaptations such as changes in Achilles tendon cross sectional area [18], stiffness [19], water content [20], and collagen organization [21]. Many of these tendon adaptations may be beneficial and improve running economy [22], improve maximal muscle power output and muscle efficiency [23], and allow the tendon to withstand increased forces over time [18] as seen in figure 1. However extreme loading forces, like those in the Achilles tendon, also contribute to maladaptation of the tendon [24] and contribute to the high injury rate of the Achilles tendon [16] as seen in figure 1. When the

Achilles tendon undergoes maladaptation, the tendon loses collagen fibril organization, experiences increased water content, and decreases in overall stiffness [25]. Having clearer understanding of harmful or beneficial adaptations within the body could help prevent Achilles tendon injury allowing people to continue to participate in beneficial exercise.

Ultrasound and magnetic resonance imaging (MRI) are imaging modalities that allow clinicians



Figure 1 – Graphical representation of Achilles tendon adaptation to strain magnitude. Appropriately stimulation of Achilles tendon properties can result in positive beneficial adaptation, however overloading can cause maladaptation of the tendon and tendon damage.

experiencing pain and loss of function [32-34].

and researchers to visualize and evaluate in-person Achilles tendon features [10, 26]. MRI provides the ability to assess tendon cross-sectional area, thickness, and T2\* time constants—which are related to tendon collagen fiber orientation and water content [27, 28]. Meanwhile, ultrasound allows for reliable and dynamic assessment of soft tissue [29-31]. Using ultrasound, clinicians and researchers can record high resolution video clips, known as Cine-loops, of the Achilles tendon giving insight into its thickness, CSA, stiffness, and water content [30]. Achilles tendon cross-sectional area, thickness, T2\* value, stiffness, and water content have all been used as tools to diagnose clinical Achilles tendinopathy in individuals already

Recent studies indicate that ultrasound imaging may be able to predict Achilles tendinopathy in individuals who are experiencing tissue maladaptation but do not yet experience pain or loss of function [35]. If this proves true, medical imaging may be sensitive to tendon adaptation processes that precede injury and dysfunction. However, other research is less certain that imaging can predict Achilles tendinopathy [36]. Refining the ultrasound and MRI techniques to identify at-risk individuals for Achilles tendinopathy would allow researchers and healthcare professionals to intervene and prevent and treat debilitating Achilles tendinopathy.

#### III. Study Hypotheses

This study hypothesizes that female athletes undergo changes in Achilles tendon water content, stiffness, and cross section in ways that are unique to the beneficial or adverse nature of the adaptation. The study further hypothesizes that MRI and ultrasound imaging are sensitive to these changes and can be used to detect and characterize the response of a tendon to loading. Finally, the study hypothesizes that female dance ensembles provide an effective environment to observe tendon adaptations.

#### IV. Study Methodology

We will test the above study hypotheses by conducting our study in three major Aims. These Aims are designed to leverage the large number of naturally occurring Achilles tendon maladaptation and tendinopathy among female dancers at BYU. They will proceed as follows:

#### Aim 1: Baseline Achilles Injury Incidence Rates

**Rationale:** While many athletic trainers and medical staff agree that the Achilles tendon injury rate among dancers is quite high, there is no generally accepted baseline injury rate. This is because existing studies are both sparse and employ different measurement methods. For example, some reports indicate that up to 33% of Irish dancers report dancing through pain, while others indicate that 80% of Irish dancers suffer lower extremity injuries [37]. The true incidence rate is difficult to establish. Here, we propose to address this gap in knowledge by measuring Achilles injury rates among female dancers at BYU. By also collecting important correlating factors (Ex. degree of cross-training, loading rates, menstrual cycle, and presence of Relative Energy Deficiency in Sport [RED-S]), the resulting data set will produce reliable and useful statistics about Achilles injury rates among otherwise healthy females for the two subsequent Aims of this study and also for researchers external to this study. The published findings will be among the first to assess the correlation between menstrual cycle phase and tendinopathy symptoms. The results are expected to have substantial impact on the field of Achilles injury.

**Experimental Methods:** We will measure tendinopathy rates utilizing undergraduate students in the office of Brenda Critchfield, the director of Dance Medicine and Wellness at BYU and a member of our study team. Her office sees hundreds of dancers who take part in BYU's numerous dance teams. Over a 12-month period, the students will assess tendons and symptomology of all interested dancers (injured and non-injured). After obtaining informed consent and with approval of the BYU Institutional Review Board (IRB), the students will collect demographic information and information about factors inherent to female dancers (such occurrence of the menstrual cycle, amenorrhea, or RED-S) via a Qualtrics survey to correlate with tendon symptoms or injury. Additionally, the students will use an ultrasound imaging device (GE Logic S8, GE Healthcare, Little Chalfont, United Kingdom) to measure echogenicity, elastic modulus (i.e., stiffness), and cross-sectional area (CSA) in both tendons in each dancer. Finally, because many dancers experience more severe symptoms in one tendon over another, the students will measure differentials in ground reaction force between each foot during a nominal dance routine. Acquired data will be audited every 3 months for completeness, conformance with ethical guidelines, and accuracy. Upon completion of collection, data will be examined for descriptive statistics and frequencies, as well as tests for normality of distribution. Correlations between assessed factors will be determined. Finally, we will calculate incidence rates and odds ratios as appropriate.

**Measures of Success:** This aim will be considered successful upon collection of Achilles injury incidence rates among a population of approximately 600 otherwise healthy dancers as well as computed correlations between the primary facts obtained in the study and the incidence rates of Achilles injury. These results will provide data to plan statistical power for the next two aims of the study.

**Potential Problems and Alternative Strategies:** Injury rates among dancers may be difficult to categorize due to the wide variety of tendon loading patterns expressed between dance genres. If this proves to be the case, we will track students taking beginning pointe, intermediate and advanced ballet, and Irish dance where students experience nearly constant tendon loading.

#### Aim 2: Healthy Adaptations to Loading

**Rationale:** This Aim intends to characterize features of healthy remodeling in female tendons. While it is currently impossible to predict whose tendons will adversely respond to changes in loading, it is possible to minimize the likelihood of adverse remodeling. For example, collegiate swimmers regularly exercise, maintain overall excellent health, and rarely experience intense Achilles tendon loading during aquatic exercise. This aim hypothesizes that the Achilles tendons of swimming athletes will undergo healthy remodeling when subjected to exercises that moderately stress the tendon. The likelihood of inducing beneficial remodeling is maximized because these individuals are otherwise healthy and the proposed exercises are moderate in intensity. Meanwhile, the tendons of healthy athletes that regularly experience high tendon loading, such as experienced dancers, should not undergo a remodeling process because the moderate intensity of the proposed exercise falls below that experienced during their normal activity. The comparison of swimmer tendons with those of dancers after conducting the same moderate exercise should elucidate features of beneficial tendon remodeling in the tendons of the swimmers.

**Experimental Methods:** Our study will recruit female swimmers (N=7) from the BYU Athletics Department and advanced pointe dancers (N=7) from BYU Theatre Ballet. Exclusion criteria will include significant cross-training, existing or recent (within the past six months) tendinopathy, and athletes who have been unable to participate in regular exercise activity for longer than seven days due to any lower extremity injury within the last three months. Over the course of 16 weeks (one semester), study participants will perform moderate daily exercises of the Achilles tendon, including plyometric jumps, eccentric heel drops, and weighted heel lifts. Participants will be given a log to record their exercise, symptoms of tendinopathy, and external factors that might independently contribute to tendon remodeling (i.e., menstrual cycle, increased preparation for performance or competition). Four times during the semester (weeks 1, 6, 11, and 16), study participants will undergo ultrasound imaging using methods as described in Aim 1. Each imaging session will include baseline imaging, a 10-minute session of moderate tendon exercise, and a repetition of imaging immediately following the exercise. This approach will identify acute and long-term exercise-induced changes to tendon biology that may contribute to tendon remodeling and correlate with other study metrics.

At weeks 1 and 16, participants will undergo an imaging session at the BYU MRI Facility (Siemens TIM-Trio 3.0T) to acquire estimates of the T2\* time constant (which acts as a surrogate for water content) in both tendons [38]. Differences in participant weight, tendon anatomy and thickness could generate large differences in tendon loading, stress, and strain during the proposed exercises and potentially confound results. To mitigate this possibility, a simplified three-component Hill-type model of the human Achillessoleus unit [37] will be used to normalize the stresses of each participant. Metrics from the imaging and exercise study will be analyzed using Mann-Whitney U-tests and mixed-model analysis of variance. **Measures of Success:** This aim will be considered successful when we have captured measurements of echogenicity, elastic modulus, T2\*, and CSA in the Achilles tendons of elite, healthy swimmers and dancers. This Aim will also produce Mann-Whitney U-test comparisons and logistic regressions of all measured features between the swimmers and the control population.

**Potential Problems and Alternative Strategies:** The one-semester time frame of the study may prove an inadequate time frame to observe remodeling of the tendon. If large changes in the tendon are observed between the first two imaging sessions, the time period until the third and fourth imaging sessions can be shortened. If the exercise produces negligible changes in tendon features in the swimming group, the exercise loading will be gradually increased until changes in tendon features are observed.

#### Aim 3: Adverse Adaptation to Loading

**Rationale:** This Aim intends to capture tendon features in individuals who are undergoing adverse remodeling processes. While the exact prevalence is to be determined in Aim 1, it is accepted among medical staff that many students within the BYU Theatre Ballet company experience Achilles pain each semester. The dance company, therefore, presents a natural laboratory for Achilles tendon maladaptation. More specifically, the Aim hypothesizes that naturally occurring changes in footwear or choreography will trigger maladaptive responses among several members of the company that, weeks later, will lead to pain and dysfunction. A carefully controlled observation during these periods should capture tendon features that are unique to maladaptation.

Experimental Methods: Investigator Shayla Bott will identify time points during the study period where the BYU Theatre Ballet Company is planning a change in choreography or footwear such that tendon maladaptation becomes likely in the normal progression of development within the company. For two weeks prior and two weeks after this time point, the study team will recruit members (N=20) of the Ballet company and collect, on a weekly basis, ultrasound data on subject's tendons using identical methods to those described in Aim 2. MRI scans will be acquired at the start and end of the study period. Because most dance choreography places larger loading on one foot over the other, we will obtain images of both right and left tendons. Prior to image acquisition, we will collect additional data about potential confounding factors including those surveyed in Aim 1. Six weeks after the final imaging session, we will conduct a follow up survey to identify which subjects developed clinical indications of tendinopathy such as tendon pain or dysfunction. After data collection, our team will separate subjects who develop tendinopathy before or at the 6-week follow-up point. As in Aim 2, loading stresses will be normalized using a 3-component model. If subjects experience symptoms in only one tendon, we will compare tendon features between the painful and nominal feet within each subject. We will also compare features between subjects who do and do not later exhibit symptoms. As in Aim 2, comparisons will be made using Mann-Whitney U-tests and multivariate logistic regression.

**Measures of Success:** This aim will be considered successful after computing Mann-Whitney comparisons and logistic regression probabilities for all collected data.

**Potential Issue and Alternative Strategies:** It is possible that many members of the dance team will be excluded from the study due to recent tendinopathy. In this case, we will expand the study to recruit subjects from intermediate ballet pointe and intermediate Irish dance classes, which experience loading and injury rates comparable to theatre ballet. To further reduce exclusion, the study will begin at the start of the 2022 and 2023 fall semesters, when dancers have likely experienced a rest period over the summer.

#### V. Expected Project Outcomes

**Planned external funding proposals**: As described in our cover page, our team plans to submit proposals for at least four external grants. All of these grants will use the results from this study as preliminary data for submission. Three minor grants (<\$100,000) will be applied for during the two-year interdisciplinary research award period. The minor grants include: 1) The Research Endowment Award sponsored by the American College of Sports Medicine that pertains to improving sports medicine. 2) The Academy of Orthopedic Physical Therapy unrestricted small grant program for research in an area examining treatment programs. 3) The American Orthopedic Foot and Ankle Society Established Research Award in the foot and ankle area. Then, near the end of the study, we will use study results as preliminary data for an NIH R01 award sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Disease.

**Planned scholarly articles** (Title, Journal, Lead Author): **1.** Incidence of Achilles Injury Among Female Dance Companies, Journal of Dance Medicine and Science, Bott. **2.** Contributing Factors to Achilles Tendinopathy among Female Dance Companies, Medical Problems for Performing Artists, Bott. **3.** Primary Image Features of Achilles Tendon Adaptation among Healthy Female Athletes, Journal of Ultrasound in Medicine; Medicine and Science in Sports and Exercise, Johnson. **4.** Inception and Development of Achilles Tendinopathy in Female Athletes, International Journal of Sports Medicine, Johnson.

**Experiential learning for at least 8 students**. One graduate student, under the supervision of Dr. Wayne Johnson, will coordinate data collection along the three study Aims. This student will coordinate with four undergraduate students working under the supervision of Shayla Bott to recruit and collect data for all study aims. Dr. Chris Dillon will supervise 2 undergraduate students as they conduct stress normalization computations. Finally, Dr. Steven Allen will supervise one graduate student to conduct MRI scans and statistical analysis.

**Improved Achilles tendinopathy treatment and prevention strategies for BYU Dance and the female athlete community**. This study will inform training regimens and therapeutic strategies that better cater to the unique physiology of female athletes. Athletes in dance, gymnastics, and other female-dominant sports that suffer Achilles injury at high rates will be able to maintain training, performance, and competition with reduced pain, resulting in uninterrupted and improved performance.

VI.	Study Schedule
e etudy	will be conducted a

This study will be conducted along the following schedule.

Study Quarter	Q1	Q2	Q3	Q4	Q6	Q7	Q8	Q9
Aim 1								
Aim 2								
Aim 3								
Manuscript Preparation								
Proposal Preparation								

# VII. Study Team

This study is led by Dr. Wayne Johnson, who possesses experience in tendon adaptation, ultrasound imaging, and epidemiological surveys. He will assist and supervise data collection and analysis. Shayla Bott is the artistic director for the BYU Theatre Ballet company and possesses experience in dance technique and biomechanics. Ms. Bott will provide access to BYU dance companies and classes, and provide technical assistance for all aims. Dr. Steven Allen possesses experience in MRI and ultrasound image acquisition and analysis. Dr. Allen will assist with all aspects of imaging and with data analysis. Dr. Chris Dillon has experience with mechanical and joint modeling and will supervise the computation and normalization of tendon stress. Finally, study member Brenda Critchfield currently serves as chief healthcare professional for all BYU dance teams. While unable to act as a primary investigator for this proposal, Ms. Critchfield possesses experience in biomechanics, sports medicine, tendon injury, and tendon rehabilitation. She will assist in subject recruitment for all study Aims, supervise data collection for all Aims, and assist with data analysis.

#### References

- 1. Cook J, Purdam CR. Is tendon pathology a continuum? A pathology model to explain the clinical presentation of load-induced tendinopathy. Br. J. Sports Med. 2009;**43**(6):409-16
- 2. de Jonge S, Van den Berg C, de Vos R-J, et al. Incidence of midportion Achilles tendinopathy in the general population. Br. J. Sports Med. 2011;**45**(13):1026-28
- 3. Lemme NJ, Li NY, DeFroda SF, Kleiner J, Owens BD. Epidemiology of Achilles tendon ruptures in the United States: athletic and nonathletic injuries from 2012 to 2016. Orthopaedic journal of sports medicine 2018;**6**(11):2325967118808238
- 4. Chan JJ, Chen KK, Sarker S, et al. Epidemiology of Achilles tendon injuries in collegiate level athletes in the United States. Int. Orthop. 2020:1-10
- Pizzolato C, Lloyd DG, Zheng MH, et al. Finding the sweet spot via personalised Achilles tendon training: the future is within reach: BMJ Publishing Group Ltd and British Association of Sport and Exercise Medicine, 2019:11-12.
- 6. Maffulli N, Testa V, Capasso G, et al. Surgery for chronic Achilles tendinopathy produces worse results in women. Disabil. Rehabil. 2008;**30**(20-22):1714-20
- Knobloch K, Schreibmueller L, Kraemer R, Jagodzinski M, Vogt PM, Redeker J. Gender and eccentric training in Achilles mid-portion tendinopathy. Knee Surg. Sports Traumatol. Arthrosc. 2010;18(5):648-55
- 8. Chan JJ, Chen KK, Sarker S, et al. Epidemiology of Achilles tendon injuries in collegiate level athletes in the United States. Int. Orthop. 2020;**44**(3):585-94
- 9. Maffulli N, Longo UG, Denaro V. Achilles tendinopathy in dancers. J. Dance Med. Sci. 2012;**16**(3):92-100
- Westh E, Kongsgaard M, Bojsen-Moller J, et al. Effect of habitual exercise on the structural and mechanical properties of human tendon, in vivo, in men and women. Scand. J. Med. Sci. Sports 2008;18(1):23-30
- 11. Bryant AL, Clark RA, Bartold S, et al. Effects of estrogen on the mechanical behavior of the human Achilles tendon in vivo. J. Appl. Physiol. 2008;**105**(4):1035-43
- Kongsgaard M, Aagaard P, Kjaer M, Magnusson S. Structural Achilles tendon properties in athletes subjected to different exercise modes and in Achilles tendon rupture patients. J. Appl. Physiol. 2005;99(5):1965-71
- 13. Ramachandran M. Basic orthopaedic sciences: CRC Press, 2018.
- Maffulli N, Sharma P, Luscombe KL. Achilles tendinopathy: aetiology and management. J. R. Soc. Med. 2004;97(10):472-6 doi: 10.1258/jrsm.97.10.472[published Online First: Epub Date]].
- 15. Wren TA, Yerby SA, Beaupré GS, Carter DR. Mechanical properties of the human achilles tendon. Clinical biomechanics 2001;**16**(3):245-51
- 16. Kannus P, Jozsa L. Histopathological changes preceding spontaneous rupture of a tendon. A controlled study of 891 patients. The Journal of bone and joint surgery. American volume 1991;73(10):1507-25
- 17. Ker R, Alexander RM, Bennett M. Why are mammalian tendons so thick? J. Zool. 1988;**216**(2):309-24
- Magnusson SP, Kjaer M. Region-specific differences in Achilles tendon cross-sectional area in runners and non-runners. Eur. J. Appl. Physiol. 2003;90(5-6):549-53

- Siu W-I, Chan C-h, Lam C-h, Lee C-m, Ying M. Sonographic evaluation of the effect of longterm exercise on Achilles tendon stiffness using shear wave elastography. J. Sci. Med. Sport 2016;19(11):883-87
- 20. Hullfish TJ, Hagan KL, Casey E, Baxter JR. Achilles Tendon Structure Differs Between Runners And Non-Runners Despite No Clinical Signs Or Symptoms Of Mid-Substance Tendinopathy. BioRxiv 2018:290866
- 21. Grosse U, Springer F, Hein T, et al. Influence of physical activity on T1 and T2\* relaxation times of healthy Achilles tendons at 3T. J. Magn. Reson. Imaging 2015;**41**(1):193-201
- 22. Roberts TJ, Marsh RL, Weyand PG, Taylor CR. Muscular force in running turkeys: the economy of minimizing work. Science 1997;**275**(5303):1113-15
- Lichtwark G, Bougoulias K, Wilson A. Muscle fascicle and series elastic element length changes along the length of the human gastrocnemius during walking and running. J. Biomech. 2007;40(1):157-64
- 24. Leadbetter WB. Cell-matrix response in tendon injury. Clin. Sports Med. 1992;11(3):533-78
- 25. Chimenti RL, Flemister AS, Tome J, et al. Altered tendon characteristics and mechanical properties associated with insertional achilles tendinopathy. J. Orthop. Sports Phys. Ther. 2014;**44**(9):680-89
- 26. Sponbeck JK, Perkins CL, Berg MJ, Rigby JH. Achilles tendon cross sectional area changes over a division I NCAA cross country season. International journal of exercise science 2017;**10**(8):1226
- 27. Juras V, Zbyn S, Pressl C, et al. Regional variations of T2\* in healthy and pathologic achilles tendon in vivo at 7 Tesla: preliminary results. Magn. Reson. Med. 2012;**68**(5):1607-13
- 28. Gärdin A, Rasinski P, Berglund J, Shalabi A, Schulte H, Brismar TB. T2\* relaxation time in Achilles tendinosis and controls and its correlation with clinical score. J. Magn. Reson. Imaging 2016;43(6):1417-22
- 29. Crofts G, Angin S, Mickle KJ, Hill S, Nester C. Reliability of ultrasound for measurement of selected foot structures. Gait Posture 2014;**39**(1):35-39
- 30. Johnson AW, Stoneman P, McClung MS, et al. Use of Cine Loops and Structural Landmarks in Ultrasound Image Processing Improves Reliability and Reduces Error in the Assessment of Foot and Leg Muscles. J. Ultrasound Med. 2019
- 31. Sponbeck JK, Frandsen CR, Ridge ST, Swanson DA, Swanson DC, Johnson AW. Leg muscle cross-sectional area measured by ultrasound is highly correlated with MRI. Journal of Foot and Ankle Research 2021;**14**(1):1-7
- Agergaard A-S, Malmgaard-Clausen NM, Svensson RB, et al. UTE T2\* mapping of tendinopathic patellar tendons: an MRI reproducibility study. Acta Radiol. 2021;62(2):215-24
- 33. Leung JL, Griffith JF. Sonography of chronic Achilles tendinopathy: a case–control study. J. Clin. Ultrasound 2008;**36**(1):27-32
- 34. Coombes B, Tucker K, Vicenzino B, et al. Achilles and patellar tendinopathy display opposite changes in elastic properties: a shear wave elastography study. Scand. J. Med. Sci. Sports 2018;**28**(3):1201-08
- 35. McAuliffe S, McCreesh K, Culloty F, Purtill H, O'Sullivan K. Can ultrasound imaging predict the development of Achilles and patellar tendinopathy? A systematic review and metaanalysis. Br. J. Sports Med. 2016;**50**(24):1516-23

- 36. Khan K, Forster B, Robinson J, et al. Are ultrasound and magnetic resonance imaging of value in assessment of Achilles tendon disorders? A two year prospective study. Br. J. Sports Med. 2003;**37**(2):149-53
- 37. Christensen SK, Johnson AW, Van Wagoner N, Corey TE, McClung MS, Hunter I. Characteristics of Eight Irish Dance LandingsConsiderations for Training and Overuse Injury Prevention. J. Dance Med. Sci. 2021;**25**(1):30-37
- 38. Nazaran A. Ultra Short MR Relaxometry and Histological Image Processing for Validation of Diffusion MRI. 2016

# Study Budget

Item	Year 1	Year 2	Total
Undergraduate Student Support (5)	\$7,000	\$12,000	\$19,000
Graduate student Support (1)	\$5,000	\$30,000	\$35,000
MRI Scanner Usage	\$7,000	\$8,000	\$15,000
Logiq E Ultrasound Device	\$35,000	\$0	\$35,000
Subject Compensation	\$5,000	\$10,000	\$15,000
Supplies	\$1,000	\$0	\$1,000
Total	\$60,000	\$60,000	\$120,000

#### **Budget Narrative**

A total of \$120,000 is requested over the two-year period of this proposal. Of this amount, a total of \$35,000 is requested to support Graduate student Joshua Sponbeck, who will be involved in all aspects of the study for 1 third of the first year and the entire second year of the study. A total of \$35,000 is requested to purchase an ultrasound imaging device for use in both Aim 1 and Aim 3. This device will be housed at the BYU Dance Medicine Facility. A total of \$19,000 is requested to support 5 undergraduates who will conduct subject recruitment, data collection, data analysis, and data presentation. A total of \$15,000 is requested to support 60 MRI scans of recruit subjects plus 8 pilot scans that will be used to ensure proper data collection. A total of \$15,000 is requested for subject compensation. Due to the burden of study tasks and the risk of exacerbating tendon injury, subjects will require a large degree of compensation to ensure compliance. Finally, a total of \$1,000 is requested to purchase supplies, such as exercise balls, for subjects to use in Aim 2.

# **Plans For External Funding**

Our assembled team will submit proposals to four external granting institutions during the award period. All of these grants will use the results from the proposed study as preliminary data for submission. Three minor grants (<\$100,000) and one major grant (>\$100,000) will be applied for. The minor grants include:

1) The Research Endowment Award sponsored by the American College of Sports Medicine. This award (\$10,000 over 1 year) funds research directly related to clinical sports medicine, including Achilles tendinopathy. While the total amount is small, it is sponsored by a prestigious organization that will grant our team a fair bit of visibility. This visibility will help our team compete against larger schools for bigger grants. Due date: January 2023.

2) The Academy of Orthopedic Physical Therapy unrestricted small grant program. This award (\$40,000 over two years) is dedicated to improving evaluation techniques for unique for research in an area examining treatment programs. Study lead Wayne Johnson has membership affiliation with each of this organizations. Due date, November 2022.

3) The American Orthopedic Foot and Ankle Society Established Research Award This award (\$50,000 over 1 year) is dedicated to research in new methods of foot and ankle care including preventative measures such as early diagnosis. Study lead Wayne Johnson has membership affiliation with each of this organization. Due date: December 2022.

4) Clinical Observational Studies in Musculoskeletal Disease (R01) award sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). This large but competitive award (\$475,000 over four years) constitutes our primary grant target. We plan to submit a proposal after gathering significant preliminary data from the proposed study. Due date: November 3, 2023

These submissions will be conducted according to the following schedule:

Study Quarter	Q1	Q1	Q3	Q4	Q5	Q6	Q7	<b>Q8</b>
ACSM								
AOPT								
AOFAS								
NIH/NIAMS								

# VIII. Biographical sketches and current and pending support for investigators on this award

#### **BIOGRAPHICAL SKETCH**

NAME: Johnson, Aaron Wayne

INSTITUTION AND LOCATION	DEGREE (if applicable)	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Brigham Young	BS	01/1992	08/1995	Pre-Physical
University, Provo, UT				Therapy/Physical
				Education
University of Alabama at Birmingham, Birmingham, AL	MS,PT	01/1996	12/1997	Physical Therapy
Brigham Young University, Provo, UT	PhD	09/2002	04/2007	Exercise Sciences- Physical Medicine and Rehabilitation

#### A. Personal Statement

I have the expertise, leadership, training, and motivation necessary to successfully carry out the proposed research project. I am a licensed physical therapist with over 20 years of clinical experience. I worked for more 10 years as a full-time physical therapist treating a variety of orthopedic, wound care, inpatient, pediatric, home health and neurologic patients. After working for 5 years, I started pursuing a terminal academic degree in Exercise Sciences with an emphasis in physical medicine and rehabilitation. I supervised multiple support staff in clinical practice and now in the research lab setting. I remain actively involved in the physical therapy profession through service in American Physical Therapy Association and by contributing to the scientific literature. I have served as Vice-President of the Utah Chapter of the American Physical Therapy Association, with responsibility for planning, managing and overseeing all aspects of the annual chapter meetings, including recruiting physical therapy scholars to provide continuing education. For past number of years my research focuses on lower extremity/foot and ankle rehabilitation and training, including tendinopathy, use of minimalist shoes, foot strengthening exercise, blood flow within the leg and foot, and plantar fasciopathy. I am trained in musculoskeletal and vascular ultrasound imaging and have experience with MR imaging. Our collaborative foot and ankle research group has produced strong publications. I understand the importance of frequent communication between project members and of developing realistic plans, timelines, budgets, and dissemination of results in the completion of studies. The current application fits with clinical and research experiences. I am currently the principle investigator at BYU on a multi-site (Universities of Wisconsin, Michigan, and North Carolina, Chapel Hill) Hamstring tendon and muscle research study funded by the National Football League.

- Christensen SK, Johnson AW, Corey Taryn E, Van Wagoner Natalie, McClung Matthew, Hunter Iain. Ground Reaction Forces of Eight Irish Dance Landings: Considerations for Overuse Injury and Training. Journal of Dance Medicine and Science. Submitted Jan 2020; Accepted April 2020, Published March 2021
- Sponbeck J\*\*, Hunter Iain, Neves Katy\*\*, Swanson Dallin C\*, Swanson Derek A\*, Johnson AW<sup>†</sup>. Achilles tendon single bout and season long adaptations during early and late collegiate

cross-country season. Physical Therapy in Sport. Jan 2021, 47:114-119. Received 27 August 2020, Revised 10 November 2020, Accepted 14 November 2020, Available online 19 November 2020 <u>https://doi.org/10.1016/j.ptsp.2020.11.028</u>

- Neves Coulter\*, Sponbeck Josh\*\*, Hunter Iain, Neves Katy\*\*, Mitchell UH, Johnson AW<sup>†</sup>. The Achilles Tendon Response to a bout of running is not affected by a triceps surae stretching training protocol in runners. Journal of Sports Science and Medicine. 19(2), 357-362, June 2020 PMID: <u>32390729</u> PMCID: PMC7196739
- 4. Adrienne D. Henderson, A. Wayne Johnson, Lindsey G. Rasmussen, Weston P. Peine, Sydney H. Symons, Kevin P. Curtis, Kade A. Scoresby, Sarah T. Ridge, Dustin A. Bruening. Early stage diabetic neuropathy reduces foot strength and intrinsic but not extrinsic foot muscle size. *Journal of Diabetes Research*. Submitted Nov 2019 Accepted Feb 2020 Volume 2020 |Article ID 9536362 | 9 pages | <u>https://doi.org/10.1155/2020/9536362</u>
- Evanson AS\*\*, Myrer JW, Eggett D, Mitchell UH, Johnson AW<sup>†</sup>. Lumbar Multifidus Muscle Size and Symmetry among Ballroom Dancers With and Without Low Back Pain. *International Journal of Sports Medicine*, 39(08): 630-635 July 2018, DOI: 10.1055/a-0631-3111
- 6. Neves KA\*\*, **Johnson AW**†, Hunter I, Myrer JW. Does Achilles tendon cross sectional area differ after downhill, level and uphill running in trained runners? *Journal of Sport Science and Medicine*, 13(4):823–828, December 2014.

# B. Positions and Honors

## **Positions and Empolyment**

1997–2002	Physical Therapist, Integrated Therapies, Madison Memorial Hospital, Rexburg, ID,			
2000-2002	Physical Therapist, Valley Home Health, Rexburg, ID			
2001-2002	Physical Therapist, Tri-County School District, St. Anthony, ID			
2002-2004	Physical Therapist, FitQuest Physical Therapy, Orem, UT			
2002-2005	Physical Therapist, Horizon Home Health, Orem, UT			
2003-2006	Physical Therapist, Sunrise Home Health, Provo, UT			
2005-2011	Physical Therapist, Central Utah Clinic, Physical Therapy, Provo, UT, (per diem)			
Assistant Professor, Department of Exercise Sciences, Brigham Young University, September 2006–				

2013

Associate Professor, Department of Exercise Sciences, Brigham Young University, September 2013–2021

Professor, Department of Exercise Sciences, Brigham Young University, Sept 2021-Present Other Experiences and Professional Memberships

1996- Member, American Physical Therapy Association

2011- Member, American College of Sports Medicine

2001-2015 Vice-President, Utah Physical Therapy Association of the American Physical Therapy

# **Honors**

College of Life Sciences – Outstanding Teaching Award

# C. Contributions to Science

I have researched factors related to running and improvement of function and performance in athletes and individuals with lower extremity injuries. The majority of these studies use musculoskeletal ultrasound imaging to assess muscle morphology. We have investigated Achilles tendon response to bouts of running in men and women collegiate cross-country runners. We studied the effect of running up and down hills on the area of the Achilles tendon, showing that the Achilles tendon decreases cross-sectional area and thins during bouts of running. The effects of stretching on Achilles tendon response to a running bout. We

#### Johnson, A W

#### ACTIVE

MSN249213 (Heiderscheit) 1.0 calendar NFL's Scientific Advisory Board (SAB) \$4,000,000 07/01/2021 - 06/30/25

Hamstring Injury (HAMIR) Index: A framework for injury mitigation strategies through innovative imaging, biomechanics, and data analytics

The purpose of this study is to investigate hamstring tendon and muscle injury risk assessment and treatment through innovative imaging, biomechanics, and data analytics

#### PENDING

1 R01 AG065674-01 (Davis) 2.0 calendar NIH \$3,263,254 Foot Health in Midlife Adults (FHIMA trial) 10/01/2022 - 09/30/2025

The purpose of this prospective, randomized control trial is to compare the effect of minimal footwear with traditional footwear on lower extremity musculoskeletal health in midlife adults

#### OVERLAP

There is no overlap between these studies

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

#### **BIOGRAPHICAL SKETCH**

NAME: Allen, Steven

INSTITUTION AND	DEGREE	END DATE	FIELD OF
LOCATION	(if applicable)	MM/YYYY	STUDY
Brigham Young University, Provo,	BS	04/2010	Physics
UT			
University of Michigan, Ann Arbor,	MS	09/2012	Biomedical
MI			Engineering
University of Michigan, Ann Arbor,	PHD	08/2015	Biomedical
Michigan			Engineering

#### A. Personal Statement

I have almost a decade's worth of experience using magnetic resonance imaging (MRI) to guide and inform focused ultrasound surgeries, including acoustics, cavitation detection, transcranial thermal ablation, histotripsy, MR physics, MR sequence development and image acquisition, and image Reconstruction. My specialty is non-thermometry-based MR guidance of focused ultrasound ablations. This work includes MR detection of cavitaiton, MR diffusion imaging to monitor thermal ablations, and MR- based detection and analysis of histotripsy lesions. I have been fortunate to obtain both education and research opportunities that allow me to understand the physics, engineering, and medical constraints of the proposed work.

1. Allen SP, Steeves T, Fergusson A, Moore D, Davis RM, Vlaisialjevich E, Meyer CH. Novel acoustic coupling bath using magnetite nanoparticles for MR-guided transcranial focused ultrasound surgery. Med Phys. 2019 Dec;46(12):5444-5453. PubMed Central PMCID: PMC6899167.

2. Allen SP, Vlaisavljevich E, Shi J, Hernandez-Garcia L, Cain CA, Xu Z, Hall TL. The response of MRI contrast parameters in in vitro tissues and tissue mimicking phantoms to fractionation by histotripsy. Phys Med Biol. 2017 Aug 18;62(17):7167-7180. PubMed PMID: 28741596.

3. Allen SP, Hernandez-Garcia L, Cain CA, Hall TL. MR-based detection of individual histotripsy bubble clouds formed in tissues and phantoms. Magn Reson Med. 2016 Nov;76(5):1486-1493. PubMed PMID: 26599823.

4. Allen SP, Hall TL, Cain CA, Hernandez-Garcia L. Controlling cavitation-based image contrast in focused ultrasound histotripsy surgery. Magn Reson Med. 2015 Jan; 73(1):204-13. PubMed PMID: 24469922.

#### B. Positions, Scientific Appointments and Honors <u>Positions and Scientific</u> <u>Appointments</u>

2020 – Present Assistant research professor, Brigham Young University, Department of Electrical and Computer engineering, Provo, UT

2020 – Visiting Professor, University of Virginia, Department of Biomedical Engineering, Charlottesville, VA

2019-2020 – Postdoctoral Research Associate, University of Virginia, Department of Biomedical Engineering, Charlottsville, VA

2017-2019 Robert M. Berne cardiovascular Research Training Grant Fellow, Cardiovascular Research Center, University of Virginia

2015 - 2016 Postdoctoral Research Scientist, Department of Biomedical Engineering, University of Virgina

#### **Honors**

2017 - 2019 Training Fellowship, Robert M Berne Cardiovascular Research Center

2015 Postdoctoral Teaching Fellowship, University of Virginia School of Engineering 2015

Summer Research Fellowship, University of Michigan Rackham Graduate School

2014 Young Investigator Award, 4th Focused Ultrasound Symposium

#### C. Contribution to Science

1. My early graduate publications focused on using Magnetic Resonance Imaging (MRI) to detect and monitor focused ultrasound histotripsy surgeries. MR monitoring of histotripsy surgeries present a unique challenge relative to monitoring thermal ablations because the the histotripsy ablation mechanism is non thermal and relies the the sub millisecond behavior of a cavitating bubble cloud. I developed an MR image acquisition method that can be sensitized to the activity of these bubble clouds, providing rapid and accurate monitoring of the treatment process.

a. Allen SP, Hernandez-Garcia L, Cain CA, Hall TL. MR-based detection of individual histotripsy bubble clouds formed in tissues and phantoms. Magn Reson Med. 2016 Nov;76(5):1486-1493. PubMed PMID: 26599823.

b. Allen SP, Hall TL, Cain CA, Hernandez-Garcia L. Controlling cavitation-based image contrast in focused ultrasound histotripsy surgery. Magn Reson Med. 2015 Jan;73(1):204-13. PubMed PMID: 24469922.

2. In addition to monitoring histotripsy bubble clouds, I was also able to develop MR imaging methods that can identify and analyze histotripsy lesions in tissues. The work involved both MR imaging development as well as tissue histology and cell microscopy work. I was able to show that different MR image contrast parameters, such is the apparent diffusion coefficient and the T2 relaxation constant, responded to different portions of the lesioning process. In particular, T2 weighted lesion contrast appeared to respond as a function of the ferritin and hemoglobin content of the treated tissue. Further, T2 contrast appeared quickly at the onset of treatment and then saturated such that further treatment could not generate more image contrast. Meanwhile, diffusion weighted lesion contrast could form irrespective of iron content and continued to change well after the T2 contrast saturated. This work will prove very useful in analyzing and predicting clinical outcomes of transcranial histotripsy surgeries.

a. Sukovich JR, Cain CA, Pandey AS, Chaudhary N, Camelo-Piragua S, Allen SP, Hall TL, Snell J, Xu Z, Cannata JM, Teofilovic D, Bertolina JA, Kassell N, Xu Z. In vivo histotripsy brain treatment. J Neurosurg. 2018 Oct 1; PubMed Central PMCID: PMC6925659.

b. Lundt JE, Allen SP, Shi J, Hall TL, Cain CA, Xu Z. Non-invasive, Rapid Ablation of Tissue Volume Using Histotripsy. Ultrasound Med Biol. 2017 Dec;43(12):2834-2847. PubMed Central PMCID: PMC5693635.

c. Allen SP, Vlaisavljevich E, Shi J, Hernandez-Garcia L, Cain CA, Xu Z, Hall TL. The response of MRI contrast parameters in in vitro tissues and tissue mimicking phantoms to fractionation by histotripsy. Phys Med Biol. 2017 Aug 18;62(17):7167-7180. PubMed PMID: 28741596.

d. Kim Y, Fifer CG, Gelehrter SK, Owens GE, Berman DR, Vlaisavljevich E, Allen SP, Ladino-Torres MF, Xu Z. Developmental impact and lesion maturation of histotripsymediated non-invasive tissue ablation in a fetal sheep model. Ultrasound Med Biol. 2013 Jun;39(6):1047-55. PubMed PMID: 23453378.

#### PROJECT/PROPOSAL CURRENT SUPPORT

1. Project/Proposal Title: ERI: Magnetic Resonance Imaging of Acoustic Fields for Ultrasound- Based CNS Regeneration

Proposal/Award Number (if available): 2138403-ERI Source

of Support: NSF/DARE

Primary Place of Performance: Brigham Young University

Project/Proposal Support Start Date (if available): 04/2022

Project/Proposal Support End Date (if available): 03/2024

Total Award Amount (including Indirect Costs): \$198,853

Person-Month(s) (or Partial Person-Months) Per Year Committed to the Project:

Year	Person- months per year
2022	<b>committed</b> 1
2023	1
2024	0.25

Overall Objectives: The goal of this project is to construct, validate, and implement a novel electromagnet that can quantify acoustic pressure fields in the CNS.

Statement of Potential Overlap: The first stage of work in this proposal has some overlap with the BYU College of Engineering MRE and seed grants. The ERI is a natural extension of the work done in the MRE and seed grants.

2. Project/Proposal Title: Mentored Research Experience: Estimating Acoustic Pressure via MRI for Improved Pediatric Brain Tumor Treatments

Proposal/Award Number (if available):

Source of Support: BYU College of Engineering

Primary Place of Performance: Brigham Young University

Project/Proposal Support Start Date (if available): 04/2021

Project/Proposal Support End Date (if available): 04/2023

Total Award Amount (including Indirect Costs): \$24,700

Person-Month(s) (or Partial Person-Months) Per Year Committed to the Project:

Year	Person-	
	months	
	per year	
	committed	
2021	0.1	
2022	0.15	



Overall Objectives: The goal of this project is to provide a mentored research environment for undergraduate engineering students at BYU. The students will design, protoype, and evaluate a novel device that can encode pressure waves into MRI scans.

Statement of Potential Overlap: Most of the mentored research experience (MRE) grant focuses on the training and support of undergraduate students. However, there is some overlap in scientific work with both the college of engineering seed fund and the first stage of the work proposed in the ERI project. This MRE grant supports undergraduates as they create the preliminary data used in the ERI proposal.

3. Project/Proposal Title: College of Engineering Seed Fund Proposal/Award Number (if available):

Source of Support: BYU College of Engineering Primary Place of Performance: Brigham Young University Project/Proposal Support Start Date (if available): 01/2021 Project/Proposal Support End Date (if available): 12/2021 Total Award Amount (including Indirect Costs): \$12,500 Person-Month(s) (or Partial Person-Months) Per Year Committed to the Project:

Year	Person-
	months
	per year
	committed
2021	0.1

Overall Objectives: The goal of this project is to develop preliminary data on the design and construction of an electromagnet that can encode pressure waves into MRI scans. Statement of Potential Overlap: There is overlap between this grant and the design section of the ERI proposal. This ERI proposal is a natural extension and expansion of the work proposed in the seed fund as befitting the nature of internal seed funding.

4. Project/Proposal Title: Comprehensive MRI Guidance of Focused Ultrasound Neurosurgery

Proposal/Award Number (if available): 1R01EB028773

Source of Support: NIH/NIBIB

Primary Place of Performance: University of Virginia

Project/Proposal Support Start Date (if available): 09/2020

Project/Proposal Support End Date (if available): 05/2024

Total Award Amount (including Indirect Costs): \$365,381

Person-Month(s) (or Partial Person-Months) Per Year Committed to the Project:

Year	Person-			
	months			
	committed			
2020	1			
2021	1			

2022	1
2023	1
2024	0.5

Overall Objectives: The overall goal of this project is to provide comprehensive MRI feedback for transcranial focused ultrasound to improve the safety, efficiency and efficacy of treatment. Statement of Potential Overlap: There is a potential overlap in effort between this grant and the ERI proposal. If the ERI grant is funded, I will reduce my effort on this grant to 0.5 person months per year.

5. Project/Proposal Title: Passive Antennas for Improved Image Quality in Transcranial MR- guided Focused Ultrasound

Proposal/Award Number (if available): 1 R21 EB029639 Source of Support: NIH

Primary Place of Performance: University of Virginia

Project/Proposal Support Start Date (if available): 05/2020

Project/Proposal Support End Date (if available): 03/2023

Total Award Amount (including Indirect Costs): \$65,855

Person-Month(s) (or Partial Person-Months) Per Year Committed to the Project:

Year	<b>Person-months</b>
	per year
	committed
Year	Person-
	months
	per year
	committed
2020	1.5
2021	0.25
2022	0.25
2022	0.25
2023	0.1
_	

Overall Objectives: The overall goal of this Trailblazer R21 project is to improve MR image quality in transcranial MR-guided focused ultrasound via the invention of passive, insertable RF reflectors

Statement of Potential Overlap: None

6. Project/Proposal Title: MRI Guidance of Focused Ultrasound Neurosurgery Proposal/Award Number (if available):

Source of Support: UVA FUS Center and Focused Ultrasound Foundation

Primary Place of Performance: University of Virginia

Project/Proposal Support Start Date (if available): 09/2019

Project/Proposal Support End Date (if available): 09/2022

Total Award Amount (including Indirect Costs): \$87,789

Person-Month(s) (or Partial Person-Months) Per Year Committed to the Project:

Year	Person-	
	months per vear	
	committed	
2019	0.15	
2020	0.15	
2021	0.15	
2022	0.15	

Overall Objectives: The goals of this project are to characterize and remove eddy current artifacts in a manner that can adapt to differences in clinical conditions that vary from site to site and to further clinical translation of 3D thermometry. Statement of Potential Overlap: None

#### PROJECT/PROPOSAL PENDING SUPPORT

1. Project/Proposal Title: Feasibility of Transcranial Histotripsy using a Hemispherical Transduce Proposal/Award Number (if available): R21EB033117

Source of Support: NIH/NIBIB

Primary Place of Performance: University of Utah

Project/Proposal Support Start Date (if available): 04/2022

Project/Proposal Support End Date (if available): 03/2024

Total Award Amount (including Indirect Costs): \$622,288

Person-Month(s) (or Partial Person-Months) Per Year Committed to the Project:

Year	Person- months per year committed
2022	0.5
2023	0.5
2024	0.5

Overall Objectives: To develop novel trans-cranial ultrasound neurosurgical tools that can be implemented in existing, clinically approved devices.

Statement of Potential Overlap: None

2. Project/Proposal Title: Iron Based Coupling Media (IBCM) for MRI-guided Transcranial Ultrasound Surgeries

Proposal/Award Number (if available): 1R01EB032773

Source of Support: NIH/NIBIB

Primary Place of Performance: Brigham Young University

Project/Proposal Support Start Date (if available): 04/2022

Project/Proposal Support End Date (if available): 03/2026 Total Award Amount (including Indirect Costs): \$2,156,748 Person-Month(s) (or Partial Person-Months) Per Year Committed to the Project:

Year	Person- months	
	per year committed	
2022	2	
2023	2	
Year	Person-	
	months	
	months per year	
	months per year committed	
2024	months per year committed 2	
2024 2025	months per year committed 2 2	

Overall Objectives: The goal of this project is to develop novel acoustic coupling media that will improve MRI guidance and safety during focused ultrasound surgical procedures. Statement of Potential Overlap: None

3. Project/Proposal Title: John A Widstoe Grant Proposal/Award Number (if available): Source of Support: BYU Office of Associate Academic Vice President

Primary Place of Performance: Brigham Young University

Project/Proposal Support Start Date (if available): 01/2022

Project/Proposal Support End Date (if available): 12/2023

Total Award Amount (including Indirect Costs): \$24,972

Person-Month(s) (or Partial Person-Months) Per Year Committed to the Project:

Year	Person-	
	months	
	per year	
	committed	
2022	0.2	
2023	0.1	

Overall Objectives: The goal of this project is to develop accelerated, nearly 3D MRI thermometry for focused ultrasound and laser thermal ablative surgeries in the brain Statement of Potential Overlap: None

#### **IN-KIND CONTRIBUTIONS CURRENT**

 Source of Support: BYU Department of Electrical and Computer Engineering Primary Place of Performance: Brigham Young University Summary of In-Kind Contributions: Support for Student Research Assistant Time Commitment - Person-Month(s) (or Partial Person-Months) Committed Per Year:

Year	Person-
	months
	per year
	committed
2021	6

Dollar Value of In-kind Contribution: \$12,500

Overall Objectives: Support of 1 undergraduate student researcher for 6 months of work. Statement of Potential Overlap: None

#### **BIOGRAPHICAL SKETCH**

#### NAME: Bott, Shayla

#### POSITION TITLE & INSTITUTION: Associate Professor, Brigham Young University A. **PROFESSIONAL PREPARATION - (see PAPPG Chapter II.C.2.f.(i)(a))**

INSTITUTION	LOCATION	MAJOR/AREA OF	DEGREE	YEAR
		STUDY	(if applicable)	(YYYY)
Utah Valley University	Orem, UT	Science (General Education)	AS	2001
University of Utah	Salt Lake City, UT	Ballet Performance	BFA	2004
University of Utah	Salt Lake City,	Ballet Pedagogy, Choreography,	MFA	2006
	UT	and Music		

#### B. APPOINTMENTS -

From - To	Position Title, Organization and Location
2018-	Associate Professor of Dance, Brigham Young University, Provo, UT
2012-2018	Associate Professor of Dance, Brigham Young University, Provo, UT
2012-2012	Visiting Assistant Professor of Dance, Brigham Young University, Provo, UT
2007-2012	Visiting Professor of Dance, Utah Valley University, Orem, UT

Current and pending for Shayla Bott:

. . . . .

	*Year (YYYY)	*Person Months (##.##)		Year (YYYY)	Person Months (##.##)
1.	2019	0.50	4.	2022	0.50
2.	2020	1.00		5.	
3.	2021	1.00			

## \*Person-Month(s) (or Partial Person-Months) Per Year Committed to the Project

1.*Project/Proposal Title :	Ballet Science: Combinin to Create Injury Resistant	g Pedagogical Tradition Dancers	with Modern Innovations
<ul> <li>Status of Support: O Current O Pending O Submission Planned O Transfer of Support Proposal/Award Number (if available): IRB X2020-313</li> <li>Source of Support: Non-financial support through Brigham Young University</li> <li>Primary Place of Performance : Brigham Young University</li> <li>Project/Proposal Start Date (MM/YYYY) (if available) : 07/2019</li> <li>Project/Proposal End Date (MM/YYYY) (if available) : 07/2022</li> <li>Total Award Amount (including Indirect Costs): \$ 0</li> </ul>			
Person-Month(s) (or Pa	rtial Person-Months) Per Yea	ar Committed to the Proj	ect
* Year (YYYY)	Person Months (##.89)	4 2022	Person Months (##.##)
2, 2020	0.00	5.	0.50
2. 2020	1.00		
*Overall Objectives :	Our motivation for condu postural and muscular del and to utilize science-bas hypothesis is as follows: i targeted muscle training, they will be stronger and	I cting this research is to f ficiencies present in pre- ed training solutions to a if pre-professional ballet specific to the individual less prone to injury.	further understand the professional ballet dancers ddress these issues. Our dancers are exposed to l during ballet class, then
*Statement of Potential Overlap :	No potential overlap		

2.*Project/Proposal Title :	Holistic Rehabilitation: a case study in physical optimization for mental health

Status of Support :	$\odot$	Current OPending	0	Submission Planned	C	Transfer of Support
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Proposal/Award Number (if available): IRB2022-008

\*Source of Support: Non-financial support from Brigham Young University

\*Primary Place of Performance : Brigham Young University

Project/Proposal Start Date (MM/YYYY) (if available) : 02/2022

Project/Proposal End Date (MM/YYYY) (if available) : 02/2023

\*Total Award Amount (including Indirect Costs): \$ 0

\*Person-Month(s) (or Partial Person-Months) Per Year Committed to the Project

*Year (YYYY)	Person Months (##.##)	Year (YYYY)	Person Months (##.##)
1. 2022	1.00	4.	
2. 2023	0.50	5.	
3.			

\*Overall Objectives : To further understand the relationship between mental health and optimal physical function. Our hypothesis is that the therapies and correctives we are using with injured dancers to correct and optimize their physical function are doing as much as or perhaps more than traditional methods of assisting dancers in improving their mental health.

\*Statement of No potential overlap Potential Overlap :

# **BIOGRAPHICAL SKETCH**

NAME: Dillon, Christopher

FIELD OF
STUDY
nanical Engineering
ngineering
guided Focused
sound
na na s

#### A. Personal Statement

The meshing of mechanical and biomedical engineering provides the opportunity to apply traditional engineering principles in novel ways to impact individuals and society for good. At Sandia National Laboratories, I worked to improve the capabilities of and validate high-fidelity computational models of assembled systems in fire environments. In my graduate and postdoctoral research, I developed techniques using magnetic resonance-guided focused ultrasound (MRgFUS) data to noninvasively characterize tissue thermal, blood flow, and acoustic properties. My experiences in thermal, biological, and mechanical modeling highlight the utility of applying a simple computational model to complex systems. For the proposed project on Achilles tendon injury, this same approach of applying a simple model is anticipated to provide fruitful insights into the complex behavior of Achilles remodeling and injury.

- 1. Dillon C, Rezvani M, McLean H, Adelman M, Dassel M, Jarboe E, Janát-Amsbury M, Payne A. A tissue preparation to characterize uterine fibroid tissue properties for thermal therapies. Med Phys. 2019 Aug;46(8):3344-3355. PubMed Central PMCID: PMC6692230.
- 2. Dillon CR, Payne A, Christensen DA, Roemer RB. The accuracy and precision of two noninvasive, magnetic resonance-guided focused ultrasound-based thermal diffusivity estimation methods. Int J Hyperthermia. 2014 Sep;30(6):362-71. PubMed Central PMCID: PMC4878146.
- Dillon CR, Todd N, Payne A, Parker DL, Christensen DA, Roemer RB. Effects of MRTI sampling characteristics on estimation of HIFU SAR and tissue thermal diffusivity. Phys Med Biol. 2013 Oct 21;58(20):7291-307. PubMed Central PMCID: PMC3864578.
- Dillon CR, Vyas U, Payne A, Christensen DA, Roemer RB. An analytical solution for improved HIFU SAR estimation. Phys Med Biol. 2012 Jul 21;57(14):4527-44. PubMed Central PMCID: PMC3402042.

#### B. Positions, Scientific Appointments and Honors <u>Positions and Scientific Appointments</u>

2021 - Assistant Professor, Brigham Young University, Mechanical Engineering, Provo,

UT 2018 - 2021 R&D S&E Computer Scientist, Sandia National Laboratories,

Albuquerque, NM

- 2014 2017 Postdoctoral Research Associate, University of Utah, Utah Center for Advanced Imaging Research, Salt Lake City, UT
- 2009 2014 Graduate Research Assistant, University of Utah, Bioheat Transfer Laboratory, Salt Lake City, UT
- 2008 2009 Research Assistant, Brigham Young University, Friction Stir Welding Laboratory, Provo, UT

#### <u>Honors</u>

2021 Employee Recognition Award, Sandia National Laboratories

2015 - 2017	F32 Kirschstein-NRSA Postdoctoral Fellowship, National Institutes
	of Health
2017	Outstanding Trainee Presentation Award, 28th Annual UCAIR
	Symposium
2017	Higher Education Teaching Specialist, University of Utah
2014	Young Investigator Award, Focused Ultrasound Foundation
2014	New Investigator Travel Award, Society for Thermal Medicine
2008	Mechanical Engineering Department Scholarship, Brigham Young
	University
2001 - 2007	Robert C. Byrd Honors Scholarship, Utah State Office of Education
2001 - 2007	Gordon B. Hinckley Presidential Scholarship, Brigham Young
	University
2001 - 2007	National Merit Scholarship, Brigham Young University

#### C. Contribution to Science

I have developed a technique to non-invasively quantify tissue acoustic and thermal properties using magnetic resonance-guided focused ultrasound (MRgFUS) temperature data. The method improved estimates of acoustic specific absorption rate (SAR) by up to 90%. I also established appropriate MR sampling characteristics to robustly apply the method and demonstrated accuracy and improved precision of thermal diffusivity measurements. These accurate non-invasive methods provide realistic patient-specific tissue property values to inform thermal models utilized in treatment planning of MRgFUS thermal therapies with the potential for increasing efficacy, reducing treatment times, and improving treatment outcomes.

- A. Dillon C, Rezvani M, McLean H, Adelman M, Dassel M, Jarboe E, Janát-Amsbury M, Payne A. A tissue preparation to characterize uterine fibroid tissue properties for thermal therapies. Med Phys. 2019 Aug;46(8):3344-3355. PubMed Central PMCID: PMC6692230. B.
- B. Dillon CR, Payne A, Christensen DA, Roemer RB. The accuracy and precision of two noninvasive, magnetic resonance-guided focused ultrasound-based thermal diffusivity estimation methods. Int J Hyperthermia. 2014 Sep;30(6):362-71. PubMed Central PMCID: PMC4878146.
- C. Dillon CR, Todd N, Payne A, Parker DL, Christensen DA, Roemer RB. Effects of MRTI sampling characteristics on estimation of HIFU SAR and tissue thermal diffusivity. Phys Med Biol. 2013 Oct 21;58(20):7291-307. PubMed Central PMCID: PMC3864578.
- D. Dillon CR, Vyas U, Payne A, Christensen DA, Roemer RB. An analytical solution for improved HIFU SAR estimation. Phys Med Biol. 2012 Jul 21;57(14):4527-44. PubMed Central PMCID: PMC3402042.

2. I have developed two novel techniques for quantifying blood flow parameters for thermal modeling of MRgFUS treatments. Because blood flow draws heat from the target region and increases treatment unpredictability, accurate heat transfer modeling of blood flow for thermal therapies is a significant and critical challenge. The techniques I have developed are a key step to eliminating the uncertainty and unpredictability that blood flow brings to thermal therapies.

- A. Shi YC, Parker DL, Dillon CR. Sensitivity of tissue properties derived from MRgFUS temperature data to input errors and data inclusion criteria: ex vivo study in porcine muscle. Phys Med Biol. 2016 Aug 7;61(15):N373-85. PubMed Central PMCID: PMC4970232.
- B. Dillon CR, Borasi G, Payne A. Analytical estimation of ultrasound properties, thermal diffusivity, and perfusion using magnetic resonance-guided focused ultrasound temperature data. Phys Med Biol. 2016 Jan 21;61(2):923-36. PubMed Central PMCID: PMC4879616.
- C. Dillon C, Roemer R, Payne A. Magnetic resonance temperature imaging-based quantification of blood flow-related energy losses. NMR Biomed. 2015 Jul;28(7):840-51. PubMed Central PMCID: PMC4510856.

PI/co-PI/Senior Personnel Name: Christopher Dillon

# Proposals/Projects

Project/Proposal Title:	BYU/SNL Reduced Order Methods Collaboration		
Status of Support:	Pending		
Proposal Award Number:	Not available		
Source of Support:	Sandia National Laboratories		
Primary Place of Performance: Brigham Young University			
Start Date:	04/2022		
End Date:	12/2022		
Total Award Amount (including Indirect Costs): \$14,999			
Time Commitment Person Months:	2022 0.25 months		
Objectives: The proposed collaboration will focus on the development of reduced order methods (ROM) that increase capacity to leverage high performance computing and advanced software tools in engineering analysis and design. We propose a thorough investigation of various linear dimensional reduction techniques and the impact of those techniques on the accuracy of the ROM.			
Statement of potential overlap: There is no overlap anticipated on these projects.			

# PI/co-PI/Senior Personnel Name: Christopher Dillon

## In Kind Contributions

Status of Support:	Current			
Source of Support:	Brigham Yo	ung University: Mechanical Engineering		
Primary Place of Performance: Brigham Young University				
Summary of In-Kind Contributions: Student Wages: \$60,000; \$20,000/year for three years Capital Equipment: \$180,000 PhD Stipend: \$8,000 Tuition: \$18,000, \$6,000/year for three years				
Dollar Value of In-Kind Cont	ribution: \$266	5,000		
Time Commitment				
Person Months:	2022	6.0 months		
	2023	6.0 months		
	2024	6.0 months		
Objectives: These funds are intended to assist Dr Dillon in establishing a research laboratory and supporting initial undergraduate and graduate student researchers in his lab. The proposed lab is a Bioheat Transfer Laboratory with emphasis in Magnetic Resonance-guided Focused Ultrasound thermal therapies. Initial objectives include developing tools for temperature- dependent tissue characterization and accurate and agile computational treatment modeling.				
Statement of potential overlap: There is no overlap anticipated on these projects.				