Kansas City Musculoskeletal Diseases Consortium
6th Annual Symposium on Musculoskeletal and Neuromuscular Diseases
UMKC – Pierson Auditorium, 5000 Holmes, Kansas City, MO
Friday, December 3, 2021
10:00 a.m. – 2:00 p.m.

10:00 am	**Welcome and Introduction of Keynote Speaker:** **Edward R. O'Connor,** PhD, MBA, FACHE, Executive Director, KCMD Consortium, Provost and Executive Vice President for Academic, Research and Student Affairs, Kansas City University
10:10 am	**Keynote Speaker: Richard J. Barohn**, MD, Executive Vice Chancellor for Health Affairs, University of Missouri - Columbia, "A Tale of 4 CIITies …. Clinical Investigator Initiated Trials"
11:00 am	**2019 and 2020 KCMD Award Winner Research Updates** Moderated by **Dr. O'Connor**
11:05 am	Abdulbaki Agbas, KCU, *"Serum Exosomal-based Biomarker Development in Canine model of ALS TDP-43 Assessment: An Update"*
11:20 am	John Stanford, KUMC, *"Unilateral Forelimb Resistance Training in an Ovariectomized Rat Model of Osteoporosis: An Update"*
11:35 am	Charlotte Phillips, MU, *"Osteogenesis imperfecta; skeletal muscle weakness, mitochondrial dysfunction, and cardiomyopathy: An Update"*
11:50 am	**Group Q&A –** Dr. O'Connor, Moderator
12:00 pm	**Lunch**
12:30 pm	**POSTER PRESENTATIONS** Elizabeth Bryda, MU, *"Rat Resource and Research Center"* Daniel Davis, MU, *"University of Missouri - Animal Modeling Core (AMC)"* Claire Houchen, UMKC, *"Jaw Bone Length is Altered by Pharmacological Inhibition of Matrix Metalloproteinase-9"*

RRNMF Neuromuscular Journal 2021;2(5):64-77

Qwynton Johnson and Alpha Bah, KCU, "*The Profile of Post-Translational Modifications of TDP-43 in Neurodegenerative Diseases: A Blood-Based Biomarker Development"*

Kevin Middleton, MU, *"Bayesian Modelling to Address the Challenges of Estimating Craniofacial Growth Patterns"*

Rose Schauffler, MU, *"Evaluation of Tibiofemoral Motion in ACL Deficient Populations"*

Colt Solberg and Bradley Thornton, KCU, *"Identification of the Human Retinal Dystrophin Promoter: Target for Treatment of Duchenne Muscular Dystrophy"*

Jacob Thomas, MU, *"Comparison of Azure Kinect and Vicon Motion Capture System for Kinematic and Spatiotemporal Evaluation of Sit-to-Stand"*

Bradley Thornton and Colt Solberg, KCU, *"Impact of Human Retinal Dystrophin Expression on Cardiomyopathy in DMD Model Mice"*

Batool Alkhamis and Wen Liu, KUMC, *"Benefits of interval walking in older people with knee osteoarthritis"*

Sara Ricardez Hernandez, MU, *"Investigating the respiratory defects in a novel patient-based spinal muscular atrophy with respiratory distress type 1 (SMARD1)"*

1:45 pm **Group Q&A –** Dr. O'Connor, Moderator

2:00 pm **Closing Remarks: Dr. O'Connor**

RRNMF Neuromuscular Journal 2021;2(5):64-77

Exosomal TAR DNA binding protein 43 profile in canine model of amyotrophic lateral sclerosis: A preliminary study in developing blood-based biomarker for neurodegenerative diseases.

Penelope Pfeiffer, DO [1], Joan R. Coates, DVM,MS,DACVIM [2], Yajaira M. Esqueda, BS[3] Andrew Kennedy, MS[3], Kyleigh Getchell, MS[3], Myra McLenon, MS[3], Edina Kosa MSc[3], Abdulbaki Agbas, MSC,PhD[3,4*]

[1]Mount Sinai Hospital, Chicago IL; [2]University of Missouri-Columbia, MO; [3]Kansas City University, Kansas City MO; [4]Heartland Center for Mitochondrial Medicine, Kansas City KS

ABSTRACT

Objective: Blood-based biomarkers provide a crucial information in progress of neurodegenerative diseases with minimally invasive sampling method. Validated blood-based biomarker application in people with amyotrophic lateral sclerosis would derive numerous benefits. Canine degenerative myelopathy is a naturally occurring animal disease model to study the biology of human amyotrophic lateral sclerosis. Serum derived exosomes are potential carriers for cell-specific cargoes making them ideal venue to study biomarkers for a variety of diseases and biological processes. This study assessed the exosomal proteins that may be assigned as surrogate biomarker that may reflect biochemical changes in central nervous system.

Methods: Exomes were isolated from canine serum using commercial exosome isolation reagents. Exosomes target proteins contents were analysed by Western blotting method.

Results: The profiles of potential biomarker candidates in spinal cord homogenate and that of serum-derived exosomes were found elevated in dogs with degenerative myelopathy as compare to control subjects.

Conclusions: Serum-derived exosomal biomolecules can serve as surrogate biomarkers in neuro degenerative diseases.

Rat Resource and Research Center

Elizabeth C. Bryda, Ph.D., Director
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The Rat Resource and Research Center (RRRC) was established in 2001 with funding from the National Institutes of Health (NIH). The goals of the RRRC are to 1) shift the burden for maintaining and distributing rat models from individual investigators to a centralized repository, and 2) provide the biomedical community with ready access to valuable rat strains/stocks and other related services that enhance the use of rats in research. Currently, the RRRC has over 540 rat lines received through active recruitment of important rat models and donations from investigators. Upon importation of strains/stocks into the RRRC, sperm and embryos are cryopreserved to ensure against future loss of the model. The RRRC distributes live animals, cryopreserved sperm and embryos as well as rat embryonic stem (ES) cell lines. Quality control measures for all materials include extensive genetic validation and health monitoring. The RRRC has unique capabilities not readily found elsewhere including, in conjunction with the MU Animal Modeling Core, the ability to make genetically engineered rat models using a variety of state-of-the-art technologies including genome editing (i.e. CRISPR/Cas9) as well as traditional methods such as random transgenesis and modified embryonic stem cell microinjection into blastocysts. Due to high success rates with intra-cytoplasmic sperm injection, the RRRC uses sperm cryopreservation as a cost-effective method for banking large collections of single gene mutations and ensuring reliable recovery when models are requested. The RRRC has expertise in rat reproductive biology, colony management, health monitoring, genetic assay development/optimization, and isolation of germline competent ES cell lines from transgenic rats; our staff and researchers are readily available for consultation and collaborations. The RRRC has a number of fee-for-service capabilities such as a wide variety of genetic analyses, cytogenetic characterization including spectral karyotype analysis, strain rederivation, strain creation, spermatozoa cryopreservation, isolation of specific rat tissues and microbiota characterization. Our website (www.rrrc.us) allows user-friendly navigation and provides information about all strains/stocks, cell lines, model donation procedures, on-line ordering, lists of services, and protocols. Current research efforts include generation and characterization of a variety of new rat models using CRISPR/Cas9 technology, refinement of models, characterization of the rat microbiota and its influence on model phenotypes, and improvements to rat in vitro fertilization. In addition to the RRRC, the University of Missouri is home to two other NIH-funded animal resources: the MU Mutant Mouse Resource and Research Center (MMRRC) and the National Swine Resource and Research Center (NSRRC) as well as the MU Metagenomics Center (MUMC) and MU Animal Modeling Core (AMC). Together, these highly collaborative groups provide a variety of animal model-related services across species to facilitate biomedical research.

MU Animal Modeling Core (AMC)

Daniel J. Davis, PhD
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Assistant Director, Animal Modeling Core
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Genome editing in animal models allows scientists to study how genes function by helping them to better understand animal and human diseases caused by specific DNA mutations or defective proteins. Genetically modified animals have been widely used in developing new treatments for conditions ranging from cancer, neurological diseases, and immune disorders to extremely rare diseases found around the world. The Animal Modeling Core (AMC) offers a wide variety of services associated with creating and characterizing genetically modified animal models. Along with traditional approaches such as random transgenesis and targeting embryonic stem cells, the AMC utilizes cutting-edge genetic modification tools such as the CRISPR/Cas system when generating animal models. CRISPR/Cas technology can be used in virtually any species and is completely customizable in regards to what genetic alterations to make. The AMC has established an efficient pipeline to create personalized human variant single nucleotide polymorphism (SNP) animal models to recapitulate specific human diseases. This pipeline includes zygote electroporation of CRISPR/Cas reagents along with a single-stranded DNA template containing the desired human variant SNP. Recently, the AMC has generated an array of personalized mouse lines modeling Spinal Muscular Atrophy with Respiratory Distress Type-1 (SMARD1). These models were generated by introducing specific human variant alleles to mimic the human disease linked to specific SNPs. These models represent the first SMARD1 mouse models that include an associated respiratory phenotype more closely recapitulating the human SMARD1 disease than past models. In conjunction with generating the SMARD1 mouse models, the AMC has created several other personalized mouse and rat models with human variant SNP alleles using this same pipeline. These types of services will further facilitate personalized medicine aspects of biomedical research.

Jaw Bone Length is Altered by Pharmacological Inhibition of Matrix Metalloproteinase-9

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Defects in craniofacial bone are one of the most common birth defects; among these are defects in jaw length (micro- and macrognathia). Micro- and macrognathia negatively affect quality of life by interfering with mastication and breathing, but the only available treatment option is multiple invasive surgeries, making ameliorative pharmacological interventions highly desirable. Lower jaw bone modeling and remodeling during development is complex and not fully understood, but previous data from our lab demonstrated a role for bone-resorbing osteoclasts in establishing lower jaw length. Matrix metalloproteinase-9 (MMP9) is a proteolytic enzyme secreted by osteoclasts during bone resorption. Aligning with known increases in osteoclast activity over the course of jaw bone development, qPCR analysis of MMP9 expression in embryonic Japanese quail (*Coturnix japonica*) lower jaws increases 34-fold from the developmental stage just prior to onset of bone resorption to the developmental stage when the facial skeleton is largely calcified ($n=7$/group, $p<0.0005$). We tested the effect of inhibiting MMP9 by delivering a single dose of a pharmacological inhibitor of MMP9 (iMMP9; 5mg/kg) to quail embryos *in ovo* over this same window of development. Morphologically normal quail have a premaxilla that extends beyond the distal tip of the lower jaw, and 90% of embryos given control saline had the normal lower jaw to premaxilla alignment ($n=16$). In contrast, 20% of iMMP9-treated quail had a lower jaw that was equal in alignment to the premaxilla and an additional 25% of iMMP9-treated quail had a lower jaw that protruded past the premaxilla ($n=20$). Control and iMMP9-treated quail skulls were scanned via microcomputed tomography and analyzed using Drishti software. iMMP9-treated quail had a significantly longer lower jaw bone than control quail, as well as a significantly higher lower to upper jaw ratio than control quail ($n=5$-6/group, $p<0.05$). Our data suggest manipulating bone resorption through pharmacological modulation of MMP9 activity is a potential option for altering lower jaw length developmentally.
Supported by the UMKC SOD Summer Scholars Program and NIH/NIDCR R03 DE031388.

The Profile of Post-Translational Modifications of TDP-43 in Neurodegenerative Diseases: A Blood-Based Biomarker Development

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ABSTRACT

Objective: To develop a blood-based biomarker for neurodegenerative diseases is a much needed tool for clinicians. Well-developed and validated blood-based biomarker will serve in early diagnosis for neurodegenerative diseases and screening purposes for patient recruitment in clinical trials. In our research, we will attempt to establish a portfolio of post-translationally modified TAR-DNA/RNA binding protein (TDP-43), a regulator of nuclear transcription factor, in platelet lysate obtained from patients with Amyotrophic Lateral Sclerosis (ALS) and agematched healthy subjects. Our aim is to identify the most prominent post-translationally modified TDP-43 derivatives as an ALS-specific biomarker and to demonstrate that such assessment can be performed in peripheral tissue such as blood. These studies will pave the road to identify disease specific TDP-43 derivative(s) that can be a potential biomarker.

Methods: Samples of ALS cytosol and age-matched controls were provided by an ALS clinic at University of Kansas Medical Center. Some platelet samples were obtained from local community blood banks for optimization studies. High-Performance Immunoprecipitation (HPIP) was utilized to enrich TDP-43 from platelet cytosol samples. The concentrated TDP-43 samples were analyzed by Western blot analysis then probed against specific antibodies including phosphorylation, ubiquitination, acetylation, cysteine oxidation, and SUMOylation. LiCor imagining and wavelength analyzing software was used to determine the level of signal intensity.

Results: The TDP-43 derived from the ALS positive sample resulted in weaker signal intensity in SUMOlyation, ubiquination, and cysteine oxidation. However, acetylation and phosphorylation of TDP-43 in the platelet cytosol obtained from patients with ALS displayed a strong signal intensity compared to the control.

Conclusion: Select post-translational modifications of TDP-43 may be used as a potential biomarker. Further validation studies and analysis must be conducted to develop potential biomarkers of ALS in the future.

Bayesian Modelling to Address the Challenges of Estimating Craniofacial Growth Patterns

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Objectives: Modelling the predicted patterns of growth in the craniofacial skeleton, both for a population and a single individual, allows estimation of peak growth velocity (PGV) and age at peak growth velocity (aPGV). Although commonly used polynomial models are flexible, they suffer from the absence of an asymptote at growth cessation. The double logistic growth model is preferred from a biological standpoint but is sensitive to its starting values, often leading to convergence failures. This study developed Bayesian multilevel double logistic growth models for linear metrics of craniofacial growth.
Methods: We studied longitudinal growth using multilevel double logistic models of 12 linear measurements using 14,891 lateral cephalograms from the Craniofacial Growth Consortium Study in females and males across ages 2.5 to 28 years (870 individuals per sex; median 9 cephalograms per individual). This model included six parameters, including an asymptotic maximum at growth cessation. Peak growth velocity (PGV) and age at peak growth velocity (aPGV) were determined via differentiation. Models were estimated using the stan programming language (ver. 2.19) in R (ver. 3.6.1), yielding posterior parameter and derived quantities of PGV and aPGV.
Results: Longitudinal growth in all measurements was successfully estimated using Bayesian inference. Across all traits, estimates of PGV and aPGV differed between females and males, with female aPGV occurring on average 2.8 years earlier and male PGV 35% faster. Population-level size at growth cessation was most variable among traits, highlighting some of the challenges of multilevel non-linear models.
Conclusions: Bayesian multilevel modelling addresses many challenges of craniofacial growth estimation using polynomials. Priors inherent to the Bayesian framework loosely constrain parameters, resulting in excellent model performance and both population- and individual-level predictions that may be used to assess growth potential and inform the timing of orthodontic treatment.

Evaluation of Tibiofemoral Motion in ACL Deficient Populations

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INTRODUCTION: Anterior cruciate ligament (ACL) injuries are one of the most common disorders of the knee with over 200,000 injuries occurring annually in the US[1]. An understanding of the normal range of tibiofemoral motion in a healthy population is necessary for identification of abnormal motions linked to ACL injury risk and pathology. Proper treatment of ACL injuries can help prevent further degenerative changes such as osteoarthritis[2]. Measurement of bone motion during dynamic activity for healthy and ACL deficient populations can differentiate pathological knee motion related to injury. While there are several technologies available to investigate tibiofemoral motion in three planes, many are limited by cost, skin artifact, and portability. This study used electromagnetic motion sensors and custom clamps to efficiently measure tibiofemoral motion in the clinic in both healthy and ACL deficient populations.
METHODS: Electromagnetic sensors were attached to 3D printed custom pieces fixated to the bony landmarks of the distal femur and proximal tibia. The femoral clamp provided a compressive fit across the condyles, while the tibial clamp was fixated immediately inferior to the tibial tuberosity on the anterior crest. A series of calibration steps and computational algorithms determined the knee axis of rotation and anatomical axes. Relative motion of the two sensors was then translated into anatomically relevant coordinates to acquire flexion-extension, varus-valgus, and internal-external rotation angles. Three cycles from each participant were used for analysis of lateral step-down and step-up and over tasks.
RESULTS: Following Institutional Review Board approval, the device was used to evaluate knee motion during functional tasks for healthy control (n=20, 14 female, 25.6 ± 5.0 years) and ACL deficient populations (n=20, 8 female, 31.3 ± 10.5 years). Comparison of cycle normalized ensemble averages showed statistically significant differences in internal-external rotation between ACL deficient and healthy populations for 90% of the cycle during step-up and over tasks and 100% of the cycle for lateral step-down tasks.
DISCUSSION: Tibiofemoral motion data was efficiently and accurately collected for both normative and pathological patients in a clinical setting. The ACL deficient group showed more external rotation during both tasks. This aligns with previous data[3]. Bilateral differences in control data may be due to inherent morphological differences[4] or task learning. Such real time data may be useful as an early screening and diagnostic tool for clinicians including physical therapists, athletic trainers, and orthopedic specialists when treating, operating on, and evaluating patients with ACL injuries.
ACKNOWLEDGEMENTS: This project was supported by the University of Missouri Coulter Biomedical Accelerator program.
REFERENCES: 1. Musahl et al (2019), N Engl J Med, 2. Van de Velde et al (2009), Arthritis and Rheumatism, 3. Bates NA, et al (2018), Clin Biomech, 4. Clement et al (2018), Gait and Posture

Identification of the Human Retinal Dystrophin Promoter: A Potential Pharmaceutical Target for Duchenne Muscular Dystrophy

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ABSTRACT

Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder that affects 1/3,500 males. Clinically, DMD presents with progressive muscle degeneration, scoliosis, loss of ambulation at twelve years of age, in addition to respiratory and cardiac complications. Death usually occurs around age twenty due to pulmonary and/or cardiac failure. Mutations that cause DMD lead to a lack of dystrophin. Currently, glucocorticoids are used to improve the patient's quality of life. There is no current cure for DMD. The goal of our research is to develop a novel pharmaceutical treatment for DMD, utilizing an isoform of human dystrophin, called retinal dystrophin (Dp260; dystrophin protein 260 kDa), that was discovered by our lab. This isoform of dystrophin contains the same functional domains as skeletal muscle dystrophin, but is smaller in size as compared to the 427 kDa muscle dystrophin and is primarily expressed in retina but not in muscle. Our lab showed that, expression of a human retinal dystrophin transgene in muscle of a DMD model mice provides health benefits with rescue of kyphosis, significantly improved cardiac and skeletal muscle, along with normal lifespan. Currently, the long range goal is to identify and characterize the promoter region driving expression of Dp260 in a cell line (that does not produce retinal dystrophin) stably transfected with an expression vector plasmid containing the promoter. This cell line will be used for high throughput screening with thousands of drugs/biological compounds to identify those that induce expression of retinal dystrophin in the muscle tissue of DMD patients.

Comparison of Azure Kinect and Optical Retroreflective Motion Capture for Kinematic and Spatiotemporal Evaluation of the Sit-to-Stand Test

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Background: The sit-to-stand test (STS) is commonly used to evaluate functional capabilities within a variety of clinical populations. Traditionally STS is a timed test, limiting the depth of information which can be gained from its evaluation. The Azure Kinect depth camera has the potential to add in-depth analysis to STS. Despite these potential benefits, the recently released (2019) Azure Kinect has yet to be evaluated for its ability to accurately assess STS.
Research Question: Purposes of this work were to compare data captured during STS using both a 12-camera Vicon motion capture system and the Azure Kinect; and to calculate kinematic and spatiotemporal variables related to the four phases of the STS cycle.
Methods: Spatiotemporal and kinematic measures for STS were simultaneously collected by both devices for 15 participants (24.15±2.32yrs., 1739.3±97.35mm). Cycle waveforms were compared for right and left hip and knee flexion/extension angular displacement, right and left hip and knee flexion/extension angular velocity, and knee-to-ankle separation ratio. Evaluated discrete outcome variables included: phase time points (the timepoints at which phases began and ended), maximum knee extension velocity from phases 3-4, medial-lateral pelvic sway range, and total time to completion. Waveform summary data were compared using R, R^2, and RMSE. Discrete variables were analyzed using Spearman's Rank correlation coefficient.
Results: R and R^2 values between the two systems indicated high levels of correlation (all R values >0.711, all R^2 values >0.660). Although there was an overall high level of agreement between waveform shapes, high RMSE values indicated some minor tracking errors for Kinect within the STS cycle. Spearman's Rank correlation coefficient indicated high levels of correlation between the systems for discrete variables (all R values >0.89), with the exception of medial-lateral pelvic sway range.
Significance: The Azure Kinect provides valuable insight into STS movement strategies allowing for improved precision in clinical decision making across multiple clinical populations.
Acknowledgements: This study was funded in part by the University of Missouri Coulter Biomedical Accelerator.
Reference:
Schenkman, M., Berger, R. A., Riley, P. O., Mann, R. W., & Hodge, W. A. (1990). Whole-body movements during rising to standing from sitting. Physical therapy, 70(10), 638-648.

Impact of Human Retinal Dystrophin Expression on Cardiomyopathy in DMD Model Mice

Bradley Thornton, M.S. Candidate, Kansas City University; Colt Solberg, M.S. Candidate, Kansas City University; Amber Wiggins-McDaniel, B.S., Kansas City University; Robert White, Ph.D., Kansas City University

ABSTRACT

Duchenne Muscular Dystrophy (DMD) is one of the most common degenerative muscle diseases that impacts approximately 1/3,500 boys. This disease results in death of the patient in the third decade of life. There is currently no cure for DMD, but therapies do exist that attempt to improve the quality of life in DMD patients. Although these therapies have some success in mitigating the disease progression, all encounter immunogenicity effects because a protein that is not endogenous is produced. To combat these challenges, our lab is studying a potential novel therapy of expressing retinal dystrophin (Dp260; Dystrophin Protein 260 kDa) in muscle as a curative treatment. A human Dp260 transgene was generated to assess the effects of expressing retinal dystrophin in muscle tissue of DMD model mice. We showed the presence of the transgene in DMD mice had significant results when comparing to DMD mice without the transgene. DMD mice exhibit scoliosis (severe curvature of the spine), cardiomyopathy, and experience a shortened lifespan (4-5 months for DMD vs. one year or more for normal mice). DMD mice that express the Dp260 Tg are rescued from almost all harmful pathological defects. Dp260 expression alters DMD mice from a lethal, severe myopathy into a mild, viable myopathy. DMD Tg mice also exhibit a normal lifespan when compared to normal control mice. The focus of my research is to collect more data on the presence of cardiomyopathy in DMD model mice and compare the cardiac tissue to DMD mice that possess the transgene. This, along with functional studies, should yield imperative data on the extent of Dp260 expression on improving the cardiomyopathy phenotype of this disease.

Interval walking effect on people with knee osteoarthritis

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Department of Preventive Medicine and Public Health

ABSTRACT

People with knee osteoarthritis (KOA) often complain the increased pain after physical exercise such as walking. A past study indicated that interval walking may reduce pain level compared to the continuous walking in people with KOA, but their intervention was only one exercise session. In this pilot randomized clinical trial, we examined the effect of interval walking (IW), and continues walking (CW) exercise for 6 weeks on the pain and fitness level of the subjects with KOA.

Sixteen participants with KOA were randomly assigned to either an IW group (n=8), or CW (n=8) group. They all completed an exercise program with 30 minutes of walking exercise, 3 times/week over a period of 6 weeks. The participants in the IW group were asked to complete the 30 minutes in 2 bouts (15 minutes each) and have 30-40 minutes resting period between the 2 bouts. The participants in the CW group were asked to walk for 30 minutes in one continuous bout. Pain level using the visual analogue scale and fitness level using the 6-minute walk test were assessed at baseline and at the end of the exercise program.

There was significant decrease ($p<0.05$) in pain level within both groups post intervention compared to baseline. There was significant difference in the change of pain score pre- to post- intervention between groups ($p<0.05$) favoring the IW group. In addition, there was significant improvement in fitness level in the IW ($p<0.01$) but not in the CW ($p=0.095$) group pre- and post-intervention. However, there was no significant between groups differences in the change of fitness level at the end of the study.

The results of our pilot trial show that walking exercise in separate interval bouts might be more effective in reduce pain and improve fitness, as compared to walking exercise in one continuous bout in people with KOA.

Investigating the respiratory defects in a novel patient-based spinal muscular atrophy with respiratory distress type 1 (SMARD1) mouse model

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Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is an infantile motor neuron disease characterized by respiratory impairment and distal muscle atrophy that results in death within 13 months of age. SMARD1 is caused by mutations in the *Immunoglobulin-m-DNA Binding Protein 2 (IGHMBP2)* gene. To better understand SMARD1 disease progression, we generated a novel mouse model *Ighmbp2*$^{D564N/D564N}$ based on the patient mutation D565N. This mutation lies within the helicase domain of IGHMBP2 and has been demonstrated to maintain the nucleic acid binding and ATPase function, but lacks helicase activity (Guenther et al., 2009). Structural studies suggest that this mutation is defective in translocating along the RNA (Lim et al., 2012).

Respiratory defects are a defining clinical symptom of SMARD1 and has not been identified in SMARD1 animal models. We assessed whether *Ighmbp2*$^{D564N/D564N}$ mice demonstrated respiratory deficiencies by conducting quantitative whole-body plethysmography on postnatal day 12 mice. Analyses were performed under normoxia and hypoxia with hypercapnia (challenge) conditions. *Ighmbp2*$^{D564N/D564N}$ mice displayed deficits in respiratory rate under both conditions, including apneas and erratic breathing, while demonstrating a higher tidal volume compared to wildtype controls. To further correlate the respiratory deficits to cellular pathology, the cervical spinal cord motor neurons were analyzed. Additionally, diaphragm neuromuscular junctions and muscle fiber size were also quantified. Currently, we are determining the extent to which the deficits exist within the respiratory pathways. By further understanding what causes the respiratory dysfunction in *Ighmbp2*$^{D564N/D564N}$ mice we can evaluate which therapeutic approaches are necessary to modify respiratory dysfunction.

•We would like to acknowledge the Animal Modeling Core at the University of Missouri for generating the Ighmbp2 models.
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