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Abstract information:

**Title:** Combinatorial neural stem cell therapy and motor rehabilitation enhance skilled task recovery after traumatic brain injury  
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Intro: Traumatic brain injury (TBI) affects nearly 1.7 million Americans each year[1,2]. Moreover, TBI creates a $7 billion strain on U.S. healthcare and economy annually due to its immediate and long-term effects[1,2]. Long-term deficits are largely due to the expansive biochemical insult that results from the initial, mechanical insult. Despite this, clinically available therapies for TBI primarily provide supportive care for the primary injury. There are currently no clinically available therapies that directly address the underlying pathologies of TBI. Preclinical studies have investigated neural stem cell (NSC) transplants to mitigate the effects of the biochemical injury with moderate success. However, the cytotoxic injury environment leads to low rates of transplant survival (2-4%) and their mechanisms of benefit are still being elucidated[3,4]. One mechanism of benefit may be promoting neuroplasticity after injury. Specifically, we have observed NSC transplants to promote recovery of the forelimb motor map area after a rodent model of TBI. However, NSC-mediated motor map recovery does not mimic native map organization and movement representation is highly variable. While NSC-mediated neuroplasticity in itself may not be sufficient to promote functional recovery, it may represent an effective neural substrate for behavioral cues. As such, we hypothesized that combinatorial NSC therapy and motor rehabilitation would enhance motor function recovery after TBI more effectively than either therapeutic approach alone.

Methods: Thirty-eight adult male Long-Evans rats received daily training on a skilled reaching task. Rats were randomly assigned to receive either sham surgery (n=10) or the controlled cortical impact (CCI) model of TBI (n=28). Two days after surgery, sham rats received intracortical injections of saline vehicle, while CCI rats were randomly assigned to receive either saline vehicle (n=9) or NSC suspension (1.8×10^5 cells in 6 μL saline; n=19). All sham and vehicle-receiving rats received daily rehabilitation on the reaching task. NSC-receiving rats were randomly assigned to receive daily (n=10) or no (n=9) rehabilitation. Non-rehabilitated rats were assessed on the reaching task once weekly. Two-way ANOVA with Tukey posthoc tests were used to assess statistical significance with α=0.05. Error shown as standard error of the mean.

Results: Sham surgeries did not significantly affect reaching (p>0.999), where the average pre- and post-surgical success rates were 88.8%±7.39% and 86.14%±9.67%, respectively. CCI surgeries led to a significant reaching impairment (p=0.0007), where pre- and post- CCI success rates were 89.30%±6.09% and 45.48%±23.12%, respectively. Both rehabilitation and NSC therapies lead to reaching improvement over baseline impairment (1.92±0.26 and 2.64±0.62 fold-increase, respectively) at the week 3 time point. Notably, the combination of NSC therapy and rehabilitation yielded significantly greater gains in reaching success rate (11.46±6.26 fold-increase over baseline impairment) compared to either NSC therapy at 3 weeks (p=0.0233) or rehabilitation at 2 and 3 weeks alone (p=0.0354).

Conclusions: These data indicate that the combination of NSC transplants and motor rehabilitation may prove more effective in promoting motor function recovery than either therapy individually. Ongoing work is investigating the capacity of behavioral cues to guide NSC-mediated neuroplasticity and transplant fate as potential mechanisms of combinatorial benefit.

Title: Evaluating the effects of gait rehabilitation on post-stroke muscle coordination

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Muscle coordination is commonly impaired post-stroke [1], but the magnitude and pattern of impairments in muscle coordination can vary across individuals, and may contribute to the variability in patient response to rehabilitation interventions. FastFES, a gait rehabilitation intervention combining fast treadmill training and functional electrical stimulation (FES), was designed to specifically target the deficits associated with abnormal plantarflexor activation during post-stroke gait. While 12-weeks of FastFES training has been shown to improve gait function, there is considerable inter-subject variability in response to the FastFES treatment, which is not fully explained by clinical or biomechanical measures of impairment [2]. Here, we present a case-series demonstrating that differential effects of FastFES on gait function in a responder and non-responder may be associated with differences in muscle coordination impairments prior to treatment. We used motor module analysis [3] to identify different patterns of muscle dyscoordination that can affect gait in post-stroke hemiparesis. Based on these preliminary results in 2 stroke survivors, we hypothesize that: 1) FastFES training can ameliorate specific muscle coordination deficits in a subpopulation of individuals with post-stroke hemiparesis; and 2) baseline muscle coordination deficits can serve as additional predictors of response to post-stroke gait training.

Two individuals greater than six months post-stroke completed a FastFES training program consisting of 18 sessions (2-3 sessions/week). Improvements in gait function were assessed using timed-up-and-go (TUG) and six-minute walk test (6MWT). Each participant also completed electromyography (EMG) testing pre- and posttraining. Participants walked overground at self-selected walking speed while EMG data were collected from 13 paretic leg muscles. Motor modules were identified from EMG using non-negative matrix factorization [3]. Our results provide evidence that different types of abnormal plantarflexor recruitment may respond differently to FastFES. Based on clinical scores, one participant was labeled a responder (TUG: 6.5 to 5.5s; 6MWT: 520.6 to 580.3m) and the other a non-responder (TUG: 24.8 to 31.7s; 6MWT: 164.9 to 139.1m). Each participant initially had different patterns of abnormal plantarflexor recruitment. In the responder, a motor module was identified pre-training with abnormal plantarflexor/dorsiflexor co-activation that was successfully unmerged with FastFES. In contrast, the non-responder initially presented with a motor module having abnormal plantarflexor/knee extensor co-activation that was not altered with FastFES. Understanding the causes of inter-individual variability in responsiveness to an intervention is a key question that, if addressed, may enable improvements in walking function and quality to be maximized at discharge from rehabilitation. Baseline muscle coordination may be an additional factor, on top of clinical and biomechanical measures, to examine contributors to inter-individual variability in responsiveness to gait rehabilitation.

References
Short-term physiologic compressive loading mitigates articular cartilage damage following traumatic impact injury in vitro

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Introduction
Osteoarthritis (OA) currently affects more than 20 million people in the United States. Approximately 12% of OA is estimated to be due to previous trauma (post-traumatic OA). Mechanical loading at low strain has been previously shown to decrease the catabolic effects of inflammatory cytokines such as IL-1 and TNF-α, however the effects of applying a physiologically relevant compressive loading protocol following a mechanical injury are currently unknown. The objective of this study was to examine the in vitro effects of a short-term, low-strain compressive loading regimen following traumatic impact injury of articular cartilage to determine if loading after injury can reduce early cartilage inflammation and degradation.

Methods
5mm diameter articular cartilage explants were harvested from the patellofemoral groove of bovine hind limbs, equilibrated in serum-free medium for 48 hours and divided into four groups: (1) impact + compressive loading; (2) impact + static culture; (3) no impact + compressive loading; (4) no impact + static culture. Groups (1) and (2) were subjected to impact injury using a custom-designed spring-loaded device delivering a 17.2 MPa force. At 24 and 48 hours following injury, groups (1) and (3) were subjected to cyclic compressive loading at 0.3 MPa and 0.5 Hz for 1 hour each day, and samples were analyzed at 72 hours post-impact. Live/Dead cell staining was performed and relative gene expression was examined by real-time RT-PCR. Additionally, glycosaminoglycan, nitric oxide and prostaglandin E2 release into the medium was quantified.

Results
Cell death decreased in samples that were subjected to cyclic loading in comparison to static controls. Gene expression for markers of cartilage degradation including matrix metalloproteases and aggrecanases, and genes involved in inflammation (COX-2, iNOS) were significantly decreased in impacted+loaded samples. Additionally, a phenotypic switch from collagen type II to collagen type I expression was prevented with loading. Significantly less GAG, nitric oxide, and PGE2 were released into the medium when impacted constructs were loaded, decreasing the values to those similar to the unimpacted controls.

Conclusions
Intermittent compression at low strains decreased impact-induced cell death and cartilage degradation in vitro at early time points. These findings suggest a potentially important role for re-establishing normal physiological loading regimens immediately following traumatic articular cartilage injury as a rehabilitative protocol that may help to prevent future development of post-traumatic osteoarthritis.
**Title:** Using Near-Infrared Imaging to Assess Knee Clearance in Rats

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**Abstract:**
Osteoarthritis (OA) is a degenerative disease of the joint that leads to joint instability, degradation of the articular cartilage surface, and eventually joint failure. The synovial membrane, which contains vascular and lymphatic capillaries, regulates the synovial fluid by controlling the influx and efflux of molecules. Protein clearance from the synovial fluid characterized as a lumped parameter that involves Starling forces, synovial permeability, and lymphatic drainage. In humans, inflammatory conditions precede the distinctive radiographic changes that confirm the loss of cartilage. The retention or clearance of inflammatory molecules like interleukin-10 (IL-10) and tumor necrosis factor alpha (TNF-α) is critical to joint health as these molecules up-regulate the synthesis of matrix metalloproteinases, which accelerate the degradation of cartilage. The objective of this study was to utilize lymphatic specific biomaterial tracers and near-infrared (NIR) imaging to determine the clearance of proteins within the knee space. NIR dye conjugated to polyethylene glycol (PEG) or albumin can be used to simulate proteins like IL-10 and (TNF-α) therefore, we have proposed a biomaterials based strategy for the determination of protein clearance. NIR imaging offers a higher temporal resolution, lower cost, minimal invasiveness, and is innocuous when compared to previously established radiolabeling techniques for intra-articular clearance measurements. OA can be surgically induced in rats via the medial meniscus transection (MMT) surgery, which involves the transection the meniscus and the medial cruciate ligament (MCL). This surgery leads to joint instability, altered loading, and presents the phenotypical cartilage degradation seen in OA at 3 weeks. The sham MMT surgery involves only the transection of the MCL and does not lead to the phenotypical cartilage damage. We hypothesize that the invasive nature of the surgery and suturing technique in the sham surgery may have an effect on the lymphatic vessels that clear the knee and thus the clearance of tracer/proteins from the knee space. Sham animals were monitored for dye clearance before (day 0) and after sham (day 2, 7, 17, 23, 46). 13kDa PEG-NIR tracer was injected into the left knees of rats to assess clearance over the course of 90 minutes. Over the time course of the sham study, there were no significant differences in clearance when compared to prior to surgery. Additionally, another study was performed to determine transport effect of tracers across a physiological size range. The results of the tracer size study show that the clearance of 13 & 40kDa PEG-NIR tracers were similar with half-lives of 129±11min and 129±37min, respectively. However, the half-life of NIR-albumin (311.2±39min) was significantly higher than the PEG-NIR tracers. Future studies will investigate whether this is a size driven phenomenon or whether alternative interactions drive the differences in clearance compared to the PEG and albumin tracers. In conclusion, our technique to measure knee clearance in rat will be used in future experiments, where we perform MMT surgery to investigate how lymphatic function and OA are linked, both in regards to the initial severity of the disease and its progression.
TITLE: Regenerative Medicine and Humanities: Novel Visions

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ABSTRACT BODY:

Purpose: To illustrate roles of health humanities and the Journal of Humanities in Rehabilitation (JHR) to deepen the connection between the science of regenerative medicine and the art of patient care.

Description: As the fields of regenerative medicine and rehabilitation merge and develop new technologies, we are reminded of the shared goal of this research – helping healing of the body and ultimately, improving the lives of those we serve. Health humanities (disciplines of humanities, social sciences and the arts) offer a language to articulate the human condition and create a greater understanding of the lived experience of these technologies. The Journal of Humanities in Rehabilitation (JHR) provides a scholarly archive for these explorations and a platform for deepening the understanding of the societal impacts of this research. The first journal devoted to humanities in rehabilitation sciences, JHR is a peer reviewed, multi-media journal using a collaborative model with rehabilitation professionals, patients and their families to gain a greater understanding of the human experience of disability through art, literature and narrative. Perspectives from the humanities can be integrated into regenerative rehabilitation in such a manner to build researcher and clinician’s critical thinking skills and foster understanding of the complex interaction of social, economic and environmental impacts of regenerative rehabilitation on health and wellness in healthcare.

Summary of Use: Engaging humanities in regenerative rehabilitation research offers novel cross-disciplinary collaborations that encourage innovation from a broad spectrum of stakeholders. Examples of these interactions presented include the ethical considerations in development and application of these technologies, concepts of visual design in complex data dissemination, using Participatory Action Research methods that involve opportunities for collaborative scholarship with research participants and the role of history in understanding context of research questions.

Importance to Members: The humanities can provide a framework to facilitate the connection of the discoveries of regenerative medicine from bench to bedside, and the realization that regenerative rehabilitation research cannot be effectively addressed out of context of health of an individual, family and society. As an interdisciplinary journal, JHR provides a unique opportunity to explore the field of regenerative rehabilitation technology through the lens of humanities, providing an added dimension of scholarship opportunities to capture the full impact of these technologies. The goal of this effort is to broaden the understanding of the concepts of humanities in rehabilitation research and create a rich breeding ground for innovative ideas to foster collaboration between the scientist, clinician and patient.
Regenerative medicine in Huntington’s disease: Optimizing rehabilitation strategies post transplantation in a rat lesion model

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Introduction: Huntington’s disease (HD) is an incurable neurodegenerative disease that causes cognitive, motor and behavioural abnormalities. Medium spiny neurons (MSNs), the most abundant cells of the striatum, degenerate in HD and cell replacement therapies aim to directly replace the degenerated MSNs in HD with healthy cells, reconnecting the lost circuitry. Preclinical studies in rodent models of HD have identified the need for extended behavioural training post transplantation to allow the recipient to ‘learn to use the graft’. Thus, after intra-striatal grafting of foetal tissue, striatally-dependent behaviours need to be re-established through targeted training, which requires appropriate integration of the graft into the host tissue. Given this evidence, it is somewhat surprising that transplantation trials in HD patients do not make any specific attempts to implement rehabilitation programmes post transplantation. Prior to the development of such rehabilitation strategies for people we must first test the feasibility and safety of when to implement such training, as well as the intensity and mode of training, in pre-clinical models of disease. Specifically training during an inappropriate time window (before the graft has connected sufficiently to the host brain) could encourage strengthening of alternative rather than striatal connections, leaving the graft redundant.

Aim: To determine the optimal time post transplantation to implement training using an animal model of HD, and in particular if training during different time windows is beneficial or detrimental to graft survival.

Method: Lister-hooded rats were pre-trained on a skilled reaching and grasping behavioural motor task that relies on intact function of the lateral striatum (n=72). After receiving unilateral striatal lesions (n=56), a subset (n=32) were grafted with rat foetal precursor striatal tissue. Thereafter, rats were re-tested on the same motor task at either 2 weeks or the gold standard 12 weeks post-graft to determine the optimal time to intervene and commence training. Histological analysis techniques will be used to determine graft survival, size and integration.

Results: All rats initially performed the motor task to a high standard. Following the lesion, this group performed significantly worse than controls when retrieving pellets using the paw contralateral to the lesion, showing a clear lesion-related motor deficit. As predicted, no significant differences between lesion and controls were seen in performance of the ipsilateral paw. The results of early post-transplantation versus late post-transplantation training on post graft performance on paw reaching will be presented at the symposium.

Conclusion: Understanding the optimal parameters for rehabilitative training post transplantation is critical to our development of cell replacement therapies. Given the encouraging pre-clinical research highlighting the importance of specific rehabilitative training post transplantation we now need to direct our attention towards when this training should be implemented, intensity and type of training. This study will help us determine if training just 2 weeks post transplantation surgery is beneficial or if this in fact promotes the strengthening of alternative circuitry given the immaturity of the transplanted tissue. This understanding will ultimately aid the development of rehabilitation strategies when moving this treatment to clinical application.
Regenerative and Rehabilitative Measures for Severe Musculoskeletal Trauma

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Orthopaedic trauma commonly involves complex musculoskeletal injuries. Comorbid skeletal muscle injuries are typically left untreated and may impair healing of fractured bone. Ultimately, patient treatment outcomes may be marginalized and costs may be increased as a result of untreated traumatized muscle tissue comorbidities. The purpose of this work was to perform initial investigations to identify plausible therapeutic approaches for severe musculoskeletal trauma with the dual intent of improving 1) bone regeneration and 2) skeletal muscle function. This investigation was performed using in a rat model of open fracture.

In all rats, a 3 mm tibia segmental defect (SD) was surgically created and stabilized with a plate (PEEK with titanium screws) in male Lewis rats (~375 g). The SD was treated with a collagen sponge carrying 1 µg of rhBMP-2 (~143 µg BMP-2/mL defect; INFUSE, Medtronic). In a subset of rats, the ipsilateral tibialis anterior (TA) muscle had a volumetric muscle loss (VML) injury surgically created with 6 mm biopsy punch and were either left unrepaired (NR) or repaired with a commercially available acellular biological matrix (SIS; Biodesign, Cook), a collagen sponge with saline (SPONGE) or an immunomodulatory drug (FK506; 10 µg), or autologous minced muscle grafts (GRAFT). Additionally, a subset of rats with SD and no repair of VML were given access to a voluntary running wheel (REHAB) beginning one week after injury. These rats ran an average of 1,411 ± 99 meters per day. All rats were assessed for bone regeneration using repeated measures µCT at 2, 4, and 6 weeks post-injury and TA muscle strength using an in vivo neural evoked isometric torque assessment 6 weeks post-injury. This study was conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for the Care and Use of Laboratory Animals.

Compared to SD-only, bone volume per total volume was reduced in the NR group by ~19, 33 and 30% at 2, 4, and 6 weeks, respectively, indicating that concomitant VML injury impaired rhBMP-2 mediated fracture healing. VML repair with SPONGE did not alter SD healing compared to the VML NR group and SIS further impaired fracture healing at 4 and 6 weeks post-injury. FK506, GRAFT, and REHAB each restored fracture healing to a similar level as observed in SD-only. Compared to SD-only, a 58% average TA muscle isometric torque deficit was observed by the NR group by 6 weeks post-injury. The SPONGE (~64%) and SIS (~53%), presented similar strength deficits. FK506 (~34%), GRAFT (~31%), and REHAB (~35%) all similarly and partially improved TA muscle strength.

These findings highlight that regenerative, immunomodulatory, and rehabilitative approaches may effectively restore rhBMP-2 mediated fracture healing that is impaired by concomitant local muscle trauma, as well as improve intermediate muscle functional outcomes. The diversity of therapies that improved bone regeneration and muscle strength suggests that multiple mechanisms of therapeutic benefit exist for severe musculoskeletal injury. Future studies will assess therapeutic synergies.

The authors declare no potential or actual conflict of interest.
The opinions or assertions contained here are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, the Department of Defense, nor the U.S. Government.
Investigation of early stages - Parkinson’s disease rat model with rotenone

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Introduction

Parkinson’s disease (PD) is a common neurodegenerative disease associated with a profound loss of dopaminergic (DA) neurons in the substantia nigra. The major clinical features include bradykinesia, rigidity, rest tremor, and postural instability. However, the onset mechanism remains to be fully understood. Note that although PD is a typical movement disorder, the majority of PD patients present with losing sense of smell or intestinal movement disorder such as constipation long before their classic clinical symptoms. Recently, Braak hypothesis (2003), neurodegeneration (accumulation of α-synuclein) begins with the dorsal nucleus of vagus nerve and the olfactory bulb and gradually spreads to the midbrain, the basal nucleus and cerebral cortex, has become more promising. This hypothesis corresponds with the clinical fact that a non-motor symptom appears prior to a motor symptom and is expected to be the key to reveal the onset mechanism of PD. In this study, we did experiment based on Braak hypothesis for the purpose of the establishment of the early stages - PD model.

Materials and methods

Male Long-Evans rats age 3 months were used for all experiments. Rotenone (2mg/kg; 2% DMSO, 98% sunflower oil) were prepared and regarded as 1 unit (1mL/kg, ip). Rats were divided into 4 groups and injected rotenone 5 days a week for 4 weeks as follows; 2 units group, 3 units group, 4 units group, control group. Concerning control group, rats were injected only vehicle. In addition, to assess behavioral deficits, Rearing test was conducted once a week. Four weeks later, rats were perfused transcardially and their brains and bowels were taken out. Brains and bowels were cut coronally at 40 µm. Afterwards immunostaining was performed to identify the existence of DA neuron and accumulation of α-synuclein. Finally, sections were collected every 200µm from rostral to caudal sequentially and observed using the optical microscope and analyzed by Image J.

Conclusion

In Rearing test, the number of exploratory behavior of the control group also decreases, but this seems to attribute to habituation. As for DA neurons, there was little change at any section in 2 units group, and there were significant degeneration not only in the olfactory bulb but also in the striatum and the substantia nigra par compacta in 4 units group. In addition, motor symptom was recognized. 3 units group, which showed prominent decrease of DA neuron in the olfactory bulb but no significant degeneration of other parts and no motor deficit, resembles the assumed pathologic findings of the early period - PD. From the above, it is indicated that 3 unit group in this study might be a PD model at the early period.
Large Animal Model Volumetric Muscle Loss Repair with Acellular Biological Scaffolds: Limitations to Functional Regeneration

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Volumetric muscle loss (VML) resulting from large-scale extremity trauma presents as chronic and persistent functional deficits, chronic disability, restricted joint range of motion, and fibrosis. Currently, there is a clinical need for therapies aimed at addressing the devastating outcomes due to VML injuries; recent investigations have examined the use of commercially available biological scaffolds as a regenerative medicine approach for VML. We hypothesized that repair of VML injuries with an acellular biologic scaffold would improve function, specifically neuromuscular strength and functional fibrosis following injury. Female Yorkshire Cross pigs (n=10) were randomized to sham or an ~20% VML injury to the peroneous tertius muscle, and injuries were left non-repaired, or surgically repaired with acellular biologic scaffold derived from either porcine small intestinal submucosa (SIS) or urinary bladder matrix (UBM) under standard clinical surgical implantation procedures. Analysis of muscle volume, muscle function via peroneal nerve stimulation, and range of motion was conducted through 12 weeks post-injury. Additionally comprehensive histopathologic investigations were conducted. Unexpected adverse advents occurred in 80% of the VML injuries repaired with the SIS scaffold. Both the repair with SIS and UBM resulted in significant fibrotic response and increased volume of the anterior compartment. However this volume could not be attributed to increased muscle, as histologic analysis of the muscle merely indicated sub-physiologic islands of muscle fibers (~50 fibers). To understand the quality of muscle, peak muscle torque was normalized to the CT-derived volume of the anterior compartment at 10 weeks post-injury, collectively in the non- and ECM-repaired limbs there was ~45% deficit compared to sham operated limbs. Additionally, in both the non- and ECM-repaired limbs there was an ~30% deficit in torque through 12 weeks post-injury. Collectively, there is no support for the capacity of ECMs to improve neural-evoked strength or result in appreciable de novo skeletal muscle regeneration after VML injury. Nonetheless, the porcine VML model does present a clinically-relevant fibrotic response and should be examined further with other regenerative rehabilitation approaches.

The authors declare no potential or actual conflict of interest. The opinions or assertions contained here are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, the Department of Defense, nor the U.S. Government.
Interaction of Injury Severity and PT Staffing in the ICU on the Mobilization of Traumatically Injured Patients: A Retrospective Study

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Purpose/Hypothesis: Traumatically-injured patients admitted to the intensive care unit (ICU) are at risk for complications secondary to prolonged immobility. Physical therapy (PT) provided in the ICU setting may be an effective means for improving functional status earlier during the patient’s course of care. The objective of this study was to determine whether the effect of full-time PT staffing in the ICU was the same on mobilization of patients with severe traumatic injuries compared to those with non-severe injuries.

Subjects: This study analyzed the medical records for all motor vehicle accident victims (n=2879) between January 2011 and September 2015 that were admitted to the 60-bed ICU at Grady Memorial Hospital, a Level-1 trauma center in Atlanta, GA. Inclusion criteria required patients to have been involved in an automobile accident, motorcycle/ATV accident, or a bicycle/pedestrian vs. automobile accident.

Materials/Methods: The patients were divided into two groups, i.e., those admitted before (n=1485) and after (n=1333) the month (i.e., June 2013) in which two full-time PT staff positions and one rehab technician position were added and dedicated to the ICU. Using Chi-square tests and 2-way (injury severity x staffing change) ANCOVAs, the two groups were contrasted on nominal and ratio variables, respectively, while examining the effect of injury severity. Injury severity was determined by the Injury Severity Scale (ISS) score. A severely injured patient was defined as one with an ISS score of >15 and a non-severely injured patient was one with a score of ≤15.

Results: For patients with non-severe injuries, the percentage of patients who were mobilized in the ICU did not change significantly from before the staffing change to afterwards (41% vs. 44%, p=0.29). On the other hand, for patients with severe injuries, the percentage of patients who were mobilized in the ICU was significantly greater after the staffing change as compared to before (60% vs. 45%, p=0.0000002). The mean (±SE) time from admission to mobilization was lower after the staffing change (6.5±0.2 vs. 7.4±0.3 days, p=0.004) but was not significantly different between patients with severe injuries and those with non-severe injuries (p=0.22).

Conclusions: In the 27 months after the initiation of full-time PT staffing in the ICU, a greater percentage of patients was mobilized in the ICU and these additional patients were mostly ones with severe injuries. The time to mobilization was lower after the staffing change but injury severity did not affect this reduction.

Clinical Relevance: Early mobilization is imperative for patients in the ICU, as complications from prolonged immobility may increase costs and length of hospital stay, and decrease patient function. Full-time PT staffing in the ICU may have a positive impact on the mobilization of severely injured patients after traumatic injury.
Five Generations: A Framework for Regenerative Stem Cell Therapies

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Objective: To summarize the current literature regarding stem cell preparation as a means to provide a novel framework for categorizing stem cells according to preparation strategy.

Methods: Selected basic science studies and clinical trials were used to illustrate the applications in each category of stem cells.

Results: A review of the literature regarding stem cell sources and preparation makes apparent that there are five generations of stem cells in various states of study and application, ranging from therapies currently being used in office-based practice to stem cell generations that hold considerable promise but with persistent concerns regarding safety and feasibility.

Conclusions: In the last decade, stem cell research has spread to many different branches of regenerative medicine. Both basic science and clinical studies examining the use of stem cell transplantation in the treatment of a wide range of human diseases have exponentially increased. The “Five Generation Model” may be a helpful way to describe stem cells in research and in clinical application. Describing stem cells in terms of cell preparation strategy, rather than source, may facilitate a greater understanding of this therapy by physicians and patients, and provides an opportunity for researchers to incorporate this helpful framework into a description of their background and findings.
Authors: LaDonya Jackson, Mohammad Sadegh Eslampanah, Maysam Ghovanloo, Lohitash Karumbaiah

Poster title: Neuromodulatory Effects of Direct Current Stimulation After a Moderate-to-Severe Traumatic Brain Injury

Abstract:

Traumatic Brain Injuries (TBI) lead to significant brain tissue damage, resulting in massive disruption of existing neural networks and consequent loss of function. There are currently no treatments to help repair disrupted neural networks and return lost function. In this study we used a controlled regimen of Direct Current Stimulation (DCS) to modulate damaged motor neurons after in vitro neurotoxicity assays, and after a moderate-to-severe TBI in a rat model. The in vitro methods will allow us to elucidate the mechanism of action underlying direct current stimulation, while the in vivo methods will allow us to elucidate the effects of DCS in mediating functional repair post-TBI.

We hypothesize that low magnitude direct current stimulation (DCS) coupled with low-frequency stimulation (LFS) of motor neurons exposed to a sub-lethal dose of a neurotoxic agent in vitro, or after a controlled cortical impact (CCI) induced TBI in rats, can help rejuvenate synaptic activation and repair. In preliminary in vitro studies a multiple electrode array (MEA) system was used to monitor baseline neuronal and neural network activation and density, and synchrony in dissociated embryonic stem cell derived GFP+ motor neurons over a period of four weeks. Preliminary results indicate that in the control groups all activity parameters increased at 2 weeks, peaked at 3 weeks and remained stable or decreased by 4 weeks post-seeding. Immunocytochemical analyses indicated decreased motor neuron density between weeks 1-3, and was accompanied by a corresponding increase in glial cell populations in the control group. When neurotoxicity was introduced at 2 weeks the electrophysiological activity at 3 and 4 weeks either dampened or diminished. We propose that the use of these defined electrophysiological parameters followed by the immunocytochemical evaluation of motor neuron cultures will allow for a robust assessment of the effects of DCS on neurons, glia, and neuronal network repair in vitro.

In preliminary in vivo studies, a custom designed wireless headstage and EnerCage system was designed to administer DCS to awake and freely moving rats. The rats were separated into 3 groups; control, TBI and Treatment (Tx). The control group only received a craniotomy, the TBI group received a craniotomy and TBI and the Tx group received a craniotomy, TBI and functional stimulation from the headstage. The animals in each group were subjected to three behavioral tasks; balance beam, rotarod and open field. The control group demonstrated superior motor control in comparison to the TBI group. On-going studies involve the application of DCS in combination with rehabilitative training to assess the extent of synaptic activation and repair. In future, we hope to converge upon an optimized DCS/behavioral training regimen that can potentially be used to repair damaged neuronal networks and restore lost function post-TBI.
Inter-Joint Coordination in Post-Stroke Gait

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Oliver Daliet, Trisha Kesar, PhD

Abstract

INTRODUCTION: The gait cycle of individuals with post stroke hemiparesis is characterized by abnormalities in both inter-joint coordination and intra-limb coordination. However, post-stroke gait is typically analyzed from phase to phase of a single joint and has no standard measure of inter-joint coordination. In this study, our purpose was to compare inter-joint coordination of the paretic and non-paretic legs of individuals with post-stroke hemiparesis.

METHODS: Using an instrumented treadmill run at a self-selected speed, gait analysis was performed on ten post-stroke individuals (> 9 month’s onset) and eight healthy, able-bodied individuals used as a control. Sagittal plane kinematic data was collected from three different walking trials and was used to calculate the average coefficient of correspondence (ACC), an alternative measurement of inter-joint coordination that quantifies the consistency of the strides across multiple gait cycles. This particular measurement was chosen for its ability to analyze multiple gait cycles simultaneously and its ease of understanding, both graphically and numerically.

RESULTS: After analyzing the data collected from the first walking trial for each participant, the results show that the ACCs in the paretic leg are significantly lower than the ACCs of the non-paretic leg for the hip-knee joints (p < 0.001). Similarly, the ACCs of the knee-ankle joints in the paretic leg were significantly lower than those of the non-paretic leg in subjects with post-stroke hemiparesis (p < 0.001).

CONCLUSION: These results show that the inter-joint coordination of the paretic leg is significantly reduced post-stroke.
Wireless Sensors to Monitor Fracture Healing
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Introduction: The clinical standard to evaluate bone fusion after common orthopaedic procedures like fracture repair and spinal fusion is computed tomographic (CT) imaging. CT is associated with a substantial radiation dose and cost, and thus its use is at most limited to a few discrete time points. Additionally, clinical rehabilitation programs to promote restoration of musculoskeletal function after fracture repair surgery (particularly polytraumatic injuries with concomitant fractures) must avoid excessive loading that could compromise mechanical integrity of the healing tissue or supplementary fixation across the fracture gap. Thus, clinicians would benefit from a non-invasive, radiation free metric to longitudinally assess the mechanical stability and progression of healing across a fusion site. To address this need, we have engineered a wireless, biocompatible strain sensor that is sufficiently small to be implanted in a pre-clinical rodent bone defect model and non-invasively quantify physiologically relevant mechanical strain across the defect gap in real-time.

Methods: Internal polysulfone fixation plates were instrumented with single-element thin-film strain sensors (Micro-measurements, 125BZ). To transmit measurements to a computer, a wireless sensor network transceiver (Texas Instruments, MSP430-RF2500) was interfaced with a custom conditioning circuit consisting of a Wheatstone bridge, a low-pass filter and a two-stage amplifier. All implanted electrical components were passivated by ISO 10993 elastomeric encapsulants. Devices were subjected to off-axis cyclic compression testing at 0.5 Hz to evaluate their sensitivity, linearity, and durability at physiological loads (n=3, strain range: 391-5162 µε, as measured by laser extensometer). A pilot surgical implantation and wireless acquisition study of the devices was completed in a critically-sized rodent 6 mm femoral bone defect model (n=3, 7 month old male Sprague-Dawley). Strain sensor data was transmitted and acquired either continuously (n=1) or intermittently (n=2, at discrete 1-2 hour periods daily) at 5-7 Hz. To evaluate the device’s ability to transmit real-time strains during functional activity, two rats were placed on a treadmill 3 days post-operatively and their gait was imaged by a high-speed bi-planar fluoroscopic system while walking at a speed of 6 m/min (producing a gait cycle of approximately 1 Hz).

Results: Sensors exhibited a sensitivity of 0.3017±0.0463 µV/µε/V, high linearity (R²=0.96-0.99), and no change in sensitivity under 5400 cycles at maximum anticipated strain. A strong signal-to-noise ratio (SNR) of the sensor readout was observed throughout the strain range (95% CI of SNR=19.86-23.53 dB at 391 µε; SNR=39.80-44.54 dB at 5000 µε). Surrogate filler materials utilized to simulate empty defects, soft tissue callus defects, and mineralized defects demonstrated the sensor can discern each stage of healing (p<0.001, all comparisons). Bi-planar fluoroscopic videos of gait correlated with real-time sensor data validated that the device measures axial deformation of the fixation plate during physiological activity. Frequency distributions of axial strain amplitudes during the gait cycles demonstrated that fixation plate strains undergo strains of up to 5000-6000 µε (Implant 1: 90th to 95th percentile = 4912 to 5443 µε; Implant 2: 90th to 95th percentile = 4855 to 6042 µε). Continuous data transmission demonstrated that a single implanted coin-cell battery can sustain 33 hours of total data transmission at 5-7 Hz.

Discussion: We have engineered a wireless strain sensor platform capable of non-invasively quantifying strain across a healing bone defect in real-time during functional activity. The device is sufficiently sensitive to the stiffness of the defect to distinguish un-mineralized and mineralized stages of fracture healing. A notable advantage of the device’s digital communication approach is its flexibility and programmability, as the battery consumption can be allocated over months by programming the on-board microcontroller for intermittent data transmission. Additional in vivo data with longer-term strain measurements is forthcoming and future work is dedicated to evaluating the device in bone defects subjected to different therapeutic treatments.
The potential role of brain-derived neurotrophic factor gene variants in rehabilitation after traumatic spinal cord injury

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Genetics may hold the key to providing targeted spinal cord injury (SCI) rehabilitation. Identifying genetic markers that predict therapy responsiveness and patient outcomes may enable greater personalization of rehabilitation strategies. One genetic marker of promise is the gene coding for the plasticity-promoting protein, brain-derived neurotrophic factor (BDNF). BDNF promotes plasticity in cultured spinal neurons, and exogenous BDNF improves motor recovery after SCI. Similarly, upregulation of bdnf mRNA via motor training (exercise) is associated with functional recovery after SCI. However, BDNF has also been linked to maladaptive processes such as spasticity and neuropathic pain, which are major complications in persons with SCI.

Do naturally occurring bdnf genes variants affect BDNF-dependent motor recovery, spasticity, and neuropathic pain after SCI? One single nucleotide polymorphism (SNP) of the bdnf gene involves a valine-to-methionine substitution at codon 66 (bdnf Val66Met). This SNP is linked to altered neuronal phenotypes associated with altered cortical plasticity, spinal plasticity, and synaptic changes following motor learning. The extent to which bdnf SNP impairs spinal plasticity in humans with SCI is unknown, but variant bdnf genes may contribute to variability in the responsiveness of persons who receive a BDNF-linked therapy such as acute intermittent hypoxia (AIH), which is known to induce spinal plasticity and subsequently enhance locomotor recovery in rodents and humans with incomplete SCI. The effect of the bdnf SNP on the likelihood of developing maladaptive BDNF-linked pain and spasticity responses is also not known. Thus, the purpose of this study was to evaluate how the bdnf SNP impacts functional outcomes and medication use for spasticity and neuropathic pain during inpatient rehabilitation following traumatic SCI. Furthermore, the potential role of genotyping in defining responders versus non-responders to AIH therapy will also be explored.

We collected genotype data from saliva samples and performed inpatient chart reviews on 42 persons with SCI. Changes in functional outcomes [i.e., American Spinal Injury Association Impairment Scale (ASIA) and Functional Independence Measure (FIM)] and medication use for spasticity and neuropathic pain were compared between persons with and without the bdnf SNP. In a subgroup of 9 persons with SCI, we also explored the possibility of an association between the presence of bdnf SNP and responsiveness to daily (5 consecutive days) AIH therapy. Each AIH therapy session included 15, 90-second bouts of hypoxia (FI0₂ = 0.09) with 60-sec intervals of normoxia (FI0₂ = 0.21).

Our results show no significant difference in change from admission to discharge neurologic level of injury, ASIA letter, total FIM scores and FIM subscores between persons with SCI with and without the bdnf SNP. However, only 40% of persons with the bdnf SNP were on neuropathic pain medications as compared to 75% of persons without the bdnf SNP. A single subject with the bdnf SNP exhibited smaller gains in walking speed after daily AIH as compared to subjects without the bdnf SNP (N=8).

This study is the first to explore genetic links involving variant forms of bdnf genotypes on motor recovery and neuropathic pain, as well as individual responses to BDNF-dependent treatments (e.g., AIH therapy) in persons with SCI. Genotyping may guide efforts to optimize and personalize the application of AIH and other rehabilitation strategies, as well as provide insight into the development of maladaptive responses such as pain. Thus, we see this preliminary effort as a unique exploration of the emerging interest in linking genomics with novel neurorehabilitation interventions such as AIH therapy.
Does effective Adapted Tango rehabilitation improve postural response modulation across stance widths in individuals with Parkinson's disease?

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Parkinson’s disease (PD) is associated with impaired postural response modulation across stance widths. PD is associated with impaired ability to decrease muscle activation upon changing from free stance to supported stance or from narrow to wide stance. Modeling and experimental results suggest that elevated muscle activation in wide stance is destabilizing and that increased postural response modulation with stance width would be associated with improved balance. Adapted Tango (AT) exercise-based rehabilitation program is effective at improving clinical measures of balance ability. It is unknown whether AT can affect postural response modulation across stance widths. Here, we hypothesized that AT would affect postural response modulation, a candidate laboratory-based rehabilitative outcome measure. Our objectives were to 1. Replicate postural response modulation deficits in PD compared to healthy individuals identified previously by Dimitrova, Henry, Horak and colleagues in lateral perturbations in a patient cohort sampled from participants in AT, and 2. Test whether postural response modulation deficits were altered after high-volume AT in a single-arm, open label pilot study.
Hematopoietic cell transplantation and enzyme replacement therapy rescue behavioral disorder and muscle weakness in Hurler mice

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Introduction: Mucopolysaccharidosis type I-Hurler (MPS I-H) is caused by a deficiency of α-L-iduronidase (encoded by IDUA gene) that leads to the accumulation of dermatan sulfate and heparan sulfate. MPS I-H results in a progressive disorder with multiple organ and tissue involvement including skeletal deformities, hearing loss, corneal clouding, heart failure and mental retardation. Currently there is no cure. Hematopoietic cell transplantation (HCT) and has been used as treatments for patients to improve visceral and neurodegenerative characteristics, except many of the musculoskeletal manifestations. In addition, enzyme replacement therapy (ERT) has proven useful in reducing non-neurological symptoms and pain. However, the treatment of combining both HCT and ERT impacting musculoskeletal functions has not been rigorously studied. Purpose: To determine the effects of HCT and ERT on musculoskeletal function in Hurler mice.

Methods: 52 Hurler mice (IDUA gene knock-out, both male and female, C57BL/6 background) were randomly assigned to groups: IV PBS only (PBS), HCT plus IV PBS (HCT+PBS), HCT plus low dose enzyme delivered IV (HCT+lowENZ) or HCT plus high dose enzyme delivered IV (HCT+highENZ); n = 11-14 per group. Wild-type C57BL/6 mice (WT, n = 7) served as the control group, which received HCT only. HCT was performed at 4-5 weeks after birth and recombinant enzyme treatment was delivered weekly (i.v. injection) for 11 mo. 24 hr cage activities and in vivo hindlimb muscle contractility were measured at 9-10 mo of age. Muscle histology was examined using hematoxylin and eosin staining.

Results: WT and HCT+highENZ mice jumped and ambulated 161-601% more than PBS and HCT+PBS mice (P≤0.046). HCT+highENZ and HCT+PBS mice had ~117% more stereotypic activity than PBS group (P≤0.042). WT and HCT+highENZ mice had 28-34% more active time and less resting time comparing with HCT+PBS mice (P≤0.026). Torque required to dorsiflex the ankle of HCT+lowENZ mice was low compared to PBS only mice (P=0.034). Peak isometric torque normalized to body mass was significantly different among all groups (P=0.016) with post hoc analysis showing that WT muscle was greater than PBS (P=0.011). H&E staining showed more organized and regular muscle fiber structure in HCT+lowENZ and highENZ groups compared to PBS group.

Conclusion: HCT plus recombinant enzyme rescued the ability of Hurler mice to be physically active, rotate the ankle, and tended to improve their muscle weakness. Understanding the effects of HCT and ERT in animal model is important for therapeutic strategies to benefit and improve daily life of Hurler patients. Supported, in part, by Genzyme, Inc.
The effect of electrical stimulation on muscle reinnervation and axon elongation in a mouse model of Val66Met

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A single nucleotide polymorphism (SNP) in the gene for brain derived neurotrophic factor (BDNF), Val66Met, results in abnormal regulated release of BDNF from neurons. The presence of this SNP could impact the translational capacity of activity-dependent treatments which enhance nerve regeneration after injury through a BDNF-dependent mechanism. We tested the effects of 1 hour of 20 Hz ES on muscle reinnervation in wild type (V/V) C578/6 mice and mice of the same background strain in which the native BDNF gene was replaced by one containing the Val66Met SNP (V/M). Sciatic nerves were cut and repaired with end-to-end anastomosis. Motor unit number estimation (MUNE) was performed using EMG recordings from lateral gastrocnemius both pre-injury and 4 weeks post-injury. Motor endplate reoccupation was evaluated using histological sections of lateral and medial gastrocnemius. From these outcome measures, our preliminary data indicate that untreated mice heterozygous for the Val66Met SNP have superior regeneration than WT mice after injury, but that treatment with ES does not further enhance their regeneration. The enhancement of regeneration in the untreated Val66Met mice may be a result of compensatory mechanisms other than BDNF that are unaffected by ES.
Changes in balance body motion and muscle activity after Adapted Tango rehabilitation for Parkinson's disease

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BACKGROUND AND AIM: Adapted tango dance (AT) has improved clinical balance and gait measures in individuals with Parkinson's disease (PD) via unknown neural mechanisms. Compared to age-matched individuals, during automatic postural responses to perturbations individuals with PD exhibit atypical electromyographic (EMG) responses with increased co-contraction between agonist and antagonist muscles and increased displacement of the center of body mass (CoM). The aim of this study was to assess the efficacy of AT in reducing co-contraction and CoM displacement during postural responses in individuals with PD.

METHODS: While ON medications, 22 participants (7 female) with mild-moderate PD (Hoehn and Yahr stages 2-3) underwent clinical assessments of PD symptoms, balance, and gait before and after high volume AT. Twenty individuals completed 15, 1.5 h lessons within 3 weeks. Of these 20 individuals, nine (2 female) participants were also assessed before and after treatment with forward and backward support-surface translation perturbations (displacement: 7.5 cm; velocity: 15 cm/s; acceleration: 0.1 g). Surface EMG from tibialis anterior (TA) and medial gastrocnemius (MG) was recorded and synchronized with kinematics and ground reaction force data. EMG onset and offset times were identified and mean EMG levels were calculated over a time window 100 - 600 ms after perturbation onset. Repeated measures ANOVAs were used to identify changes in clinical measures and reactive balance measures after AT. Spearman correlations were used to determine the association of change in clinical measures with change in reactive balance measures.

RESULTS: At post-testing, participants (n=20) improved on the Berg Balance Scale (p<0.001; effect size d=0.66), Fullerton Advanced Balance Scale (p<0.001; d=0.55), Dynamic Gait Index (p<0.01; d=0.53), preferred (p<0.01; d=0.54) and fast cadence (p=0.03; d=0.44), and Unified Parkinson's Disease Rating Scale Motor Subscale-III (p<0.01; d=0.42). Participants in the reactive balance group (n=9) also exhibited significant reductions in peak CoM displacement (p=0.03; d=-0.26), increases in antagonist onset time (p<0.03; d=0.60) and decreased agonist EMG mean level (p=0.03; d=-0.52) during support surface perturbations. Significant correlations were identified between changes in reactive balance measures and changes in clinical measures, including between BBS and CoM displacement (rho=-0.68; p=0.04) and antagonist offset time (rho=0.84; p=0.04).

CONCLUSIONS: Adapted tango beneficially altered clinical measures of balance ability, reduced CoM displacement and may have potentiated reduced co-contraction during postural responses to perturbations. Studying neuromuscular activity before and after balance rehabilitation may provide insight into potential neural mechanisms underlying the recovery of balance in individuals with PD through rehabilitative means.
Statistically-significant contrasts between EMG waveforms revealed using wavelet-based functional ANOVA

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We developed wavelet-based functional ANOVA (wfANOVA) as a novel approach for comparing neurophysiological signals that are functions of time. Temporal resolution is often sacrificed by analyzing such data in large time bins, increasing statistical power by reducing the number of comparisons. We performed ANOVA in the wavelet domain, because differences between curves tend to be represented by a few temporally-localized wavelets, which we transformed back to the time domain for visualization. We compared wfANOVA and ANOVA performed in the time domain (tANOVA) on both experimental EMG signals from responses to perturbation during standing balance across changes in peak perturbation acceleration (three levels) and velocity (four levels), and on simulated data with known contrasts. In experimental EMG data, wfANOVA revealed the continuous shape and magnitude of significant differences over time without a priori selection of time bins. However, tANOVA revealed only the largest differences at discontinuous timepoints, resulting in features with later onsets and shorter durations that those identified using wfANOVA (p<0.02). Further, wfANOVA required significantly fewer (≈1/4×, p<0.015) significant F-tests than tANOVA, resulting in post-hoc tests with increased power. In simulated EMG data, wfANOVA identified known contrast curves with a high level of precision (R2=0.94±0.08), and performed better than tANOVA across noise levels (p<<0.01). Therefore, wfANOVA may be useful for revealing differences in the shape and magnitude of neurophysiological signals (e.g. EMG, firing rates) across multiple conditions with both high temporal resolution and high statistical power.
Engineering Pre-Vascularized Skeletal Muscle with Physiologically-Relevant Cellular Organization for Treatment of Volumetric Muscle Loss

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Introduction: Vascular disease or traumatic injury often results in impaired endogenous tissue regeneration and revascularization capacity. A successful therapeutic intervention must augment vascularization and tissue function, while also restoring physiological anatomical structure. Towards this goal, we bioengineered parallel-aligned skeletal muscle constructs that mimic the physiological orientation of native vasculature and muscle tissue, to examine their therapeutic potential in a model of vascular and muscular injury. We hypothesized that co-culture of vascular endothelial cells (ECs) with skeletal muscle myoblasts on highly ordered three-dimensional scaffolds will produce parallel-aligned myotubes interspersed with aligned capillary-like structures that augment muscle regeneration in vivo.

Materials and Methods: Aligned collagen scaffolds were fabricated by extruding high concentration rat-tail collagen type I (30 mg/mL) from 22G blunt tip needles at a rate of 3.2mL/min into pH neutral buffer to initiate fibrillogenesis. Non-aligned (randomly-oriented) collagen strips were similarly made by extrusion at a decreased speed. For cell culture studies, approximately 500,000 fluorescently labeled (GFP+/luc+) mouse myoblasts (C2C12) were seeded on each parallel-aligned nanofibrillar scaffold or non-aligned scaffold (control). Myoblasts were differentiated into myotubes with media containing 3% horse serum for 6 days. After differentiation, 500,000 fluorescently labeled (mRuby+) human ECs (HMEC-1 cell line) were co-cultured with the myoblasts for an additional 3 days. The mechanical function of constructs was assessed with a 1Hz electrical stimulation. Constructs were fixed for immunofluorescent staining of myosin heavy chain and CD31 and confocal tile-stitched images were analyzed in imageJ for quantification of myotube orientation, length, and nuclear incorporation. For in vivo studies, constructs were transplanted into a mouse model of volumetric muscle loss (VML) that was created by surgical excision of 20% of the anterior tibialis (TA) muscle. Constructs were sutured at the distal and proximal ends of the defect followed by suture closure of the muscle and skin flaps. Bioluminescent imaging (BLI) was performed on days 0, 7, 14, and 21 of the study. On day 21, the TA muscle was extracted and processed for histological analysis.

Results and Discussion: Seeded myoblasts and ECs became highly aligned along the direction of the nanofibrillar scaffolds (4.9±1 angle of orientation), in comparison to cells grown on non-aligned scaffolds (40.1±4 angle of orientation). Average myotube lengths and nuclei incorporation on aligned scaffolds were 2 times greater than on non-aligned scaffolds. Upon in vitro electrical stimulation, aligned muscle constructs demonstrated coordinated contraction properties compared to non-aligned constructs. Fluorescently labeled aligned or randomly oriented engineered muscle constructs were transplanted into the defect of a murine VML model for 21 days. Based on immunohistochemical analysis of skeletal muscle myosin and CD31 for visualization of regenerated muscle and ECs, respectively, the region of tissue injury treated with constructs composed of aligned myoblasts and ECs demonstrated significantly more re-vascularization and improved muscle regeneration, compared with non-aligned and cell-free constructs.

Conclusions: This work demonstrates that pre-vascularized engineered muscle tissue using ECs on aligned nanofibrillar scaffolds, mimics the spatial organization of native muscle and has important translational potential as a muscle graft to enhance muscle regeneration in a diseased injury model.
Title: Whole-body vibration training in healthy males promotes stem/progenitor cell circulation and decreased inflammation levels

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Purpose/Hypothesis: Cardiovascular disease (CVD) is the leading cause of death in the United States. Despite the benefits of exercise in this and other populations, adherence to exercise programs is often problematic. The purpose of this pilot study was to determine the effects on whole-body vibration training on biomarkers associated with CVD. We hypothesized that vibration training in healthy males would increase acute mobilization of peripheral blood (PB) stem/progenitor cells into circulation and decrease inflammatory marker levels.

Subjects: 11 healthy males, 18-30y (n=6) and 50-65y (n=5) (BMI ≥ 18 ≤ 25 kg/m²), were recruited.

Materials/Methods: Baseline vitals and PB samples were obtained upon informed consent. Participants were assigned to perform all three of the following activities in random order on separate days (4-7d intervals): A) standing on a vibrating platform only; B) repetitive, intensive, dynamic leg squat exercise (wearing a weighted body vest = 15% body weight); and C) in combination, i.e. same exercise on a vibrating platform. Vitals and PB samples were taken again post-activity. PB mononuclear cells were isolated and cell populations from the lymphocyte fraction were characterized based on their phenotypic properties utilizing a validated, polychromatic flow cytometry protocol with appropriate controls. Enzyme-linked immunosorbent assays were used to determine growth factor and inflammatory marker plasma concentration levels. Main outcome measures were analyzed using paired t-tests (p<0.05).

Results: Angiogenic circulating progenitor cells (CPCs) (CD31+CD34brightCD45dim) increased 33% (p=0.02) with vibration alone; a similar effect was found with exercise plus vibration in that angiogenic CPCs increased 34% (p=.04); while less of an increase, 21%, was realized with leg squats alone (p=.02). VEGF levels were significantly higher with vibration alone (p<0.005); TNFα increased significantly with vibration (p<0.01); IL-6 approached a significant drop during vibration (p<0.056); and significantly higher levels of IL-10 were found with vibration alone (p<0.03) and squat-only (p<0.05), but interestingly, a significant decrease in IL-10 level was found when exercise and vibration were combined. Age effects were not determined.

Discussion/Conclusions: CPC levels increased with vibration alone more than with leg squatting exercise alone and nearly the same as when combined with exercise. Findings suggest vibration alone may have a pro-angiogenic effect taken together with higher VEGF and TNFα levels; more than with exercise alone or in combination. Furthermore, vibration alone may have greater anti-inflammatory effects as evidenced with a trend in decreased inflammatory marker (IL-6) and a significant increase in anti-inflammatory marker (IL-10) levels. Curiously, the anti-inflammatory effect was dampened when vibration was combined with exercise in that the drop in IL-6 did not approach significance and IL-10 levels were actually lowered; suggesting there may be a threshold for the optimal dose and/or combination effects. Future research should consider optimal data collection time points and dose response.

Clinical Relevance: The benefits of exercise have long been determined, but when this is not possible or difficult, it becomes important to find other ways to gain similar effects. Preliminary findings from this study indicate vibration protocols as an exercise surrogate may offer a viable option to increase stem/progenitor cell circulation levels and decrease inflammation with possible health benefits in CVD and other conditions.
References:


Novel rehabilitation techniques to improve muscle function following volumetric muscle loss injuries.

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Volumetric muscle loss (VML) injuries include traumatic or surgical skeletal muscle removal and result in extensive functional impairments. Following VML injuries, muscle repair processes are restricted by prolonged inflammation, increased fibrosis, and a lack of de novo muscle regeneration. Augmenting mitochondrial capacity and intermittent electrical stimulation has been shown to be an effective strategy to enhance functional muscle regeneration; however, the extent to which these rehabilitative strategies work after VML have not been tested. Additionally, current rehabilitation techniques (e.g., range of motion) to treat VML injuries begin several months after the injury and do not target cellular or physiological pathways to improve muscle function. Therefore, a primary objective of this study was to determine if early intervention rehabilitation promotes functional regeneration. We hypothesized that early rehabilitation interventions involving range of motion, muscle stimulation, and cellular targeting to augment mitochondrial capacity (via guanidinopropionic acid, GPA) would improve function of the remaining tissue following VML injury. We studied three different early rehabilitation interventions using a multi-muscle (gastrocnemius and soleus) model of VML injury in the hindlimb of mice. Mice underwent a ~20% VML injury and were then randomized into three rehabilitation groups; range of motion exercise (ROM) used as a clinical rehabilitation control, range of motion with intermittent electrical stimulation (ROM+ESTIM), and range of motion with electrical stimulation and 1% GPA chow (ROM+ESTIM+GPA). All rehabilitation interventions were started 72 hours after the VML injury. Mice underwent two bouts of 30-minute therapy sessions per week. For each rehabilitation session, passive muscle torque, a measure of muscle stiffness, was recorded. Following 1, 2 and 4 months of rehabilitation peak isometric torque and sub-maximal isometric torques analyzed as a function of stimulation frequency were assessed in vivo. After two months of rehabilitation, peak isometric torque of the plantarflexor muscles was significantly greater in both the ROM+ESTIM and ROM+ESTIM+GPA rehabilitation groups compared to ROM alone (p=.0212). Additionally, sub-maximal isometric torques, analyzed as a function of stimulation frequency, were significantly less in the ROM group compared to ROM+ESTIM and ROM+ESTIM+GPA (p=.0383). Preliminarily results indicated that passive muscle torque decreased throughout individual PT sessions in all rehabilitation groups (~15-40%). Preliminary findings also suggest that passive torque declined with each week of rehabilitation for both ROM and ROM+ESTIM groups. Overall, these preliminary findings suggest that introducing early rehabilitation approaches improves functional regeneration of the remaining tissue following VML injury. Specifically, range of motion interventions may lessen passive stiffness promoting joint mobility, and introducing an early muscle stimulation intervention appears to enhance the function (i.e., torque) of the remaining tissue at 2 months following VML injury. Further research needs to be solicited to determine whether there is an additive benefit of augmenting mitochondrial capacity in the remaining muscle tissue after VML injury.
The effect of motor state on LTP-like corticomotor neuroplasticity induced by paired associative stimulation

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Introduction: Repeated pairing of electrical stimulation of a peripheral nerve with transcranial magnetic stimulation (TMS) over the primary motor cortex (M1) representation for a target muscle can induce neuroplastic adaptations in the human brain. Currently, it is unclear if motor state of the targeted muscle during this form of paired associative stimulation (PAS) influences the induction of long-term potentiation (LTP)-like plasticity. Additionally, the distinct underlying neural contributions to LTP-like plasticity during active versus resting motor states is poorly understood. Here, we investigated the effect of motor state during PAS on measures of general corticomotor excitability and intracortical circuit excitability.

Methods: Eleven young, neurologically-intact participants completed three separate visits separated by at least one week, each consisting of one of three PAS protocols: PASREST (no active contraction in the left abductor pollicis brevis [APB]), PASACTIVE (10% maximal voluntary contraction [MVC] of the left APB), and PASCONTROL (10% MVC of left APB paired with sham TMS). PAS consisted of 180 pairs of left median nerve stimulation (at just above APB motor threshold) followed by TMS over contralateral M1 (at an intensity to elicit a 1mV motor evoked potential [MEP] in APB muscle), with an inter-pulse interval based on the individual N20 latency + 5ms delivered at 0.25Hz. Measures of general corticomotor excitability (MEP peak-to-peak amplitude), intracortical facilitation (ICF) and short interval intracortical inhibition (SICI) were collected prior to PAS, directly following PAS and at 30 and 60min post-PAS.

Results: Following PASREST and PASACTIVE there was an increase in MEP amplitude across all post-testing time points. A change in MEP amplitude was not observed following PASCONTROL. Additionally, we observed an increase in ICF and decrease in SICI following the PASACTIVE protocol that was not present following PASREST or PASCONTROL.

Discussion: Preliminary results of this study suggest that PAS during both active and resting motor states produces LTP-like increases in general corticomotor excitability. Interestingly, the effect of PAS under different motor states likely occurs through different neural mechanisms of intracortical excitation and inhibition. Consistent with previous literature, we observed high inter-individual variability in response to PAS for each protocol and evaluation of individual response profiles may provide additional information to guide future PAS interventions during active and resting motor states. These results may have important implications for understanding the capacity for inducing functional neuroplastic change to improve rehabilitation outcomes in patients with various neuropathologies.
Daily exposure to acute intermittent hypoxia with walking practice enhances walking ability in persons with chronic incomplete spinal cord injury

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Neural plasticity contributes significantly to walking recovery after incomplete spinal cord injury (iSCI). Therapies that augment endogenous mechanisms of plasticity are viable tools to restore walking in persons with SCI. Breathing mild bouts of low oxygen (i.e. acute intermittent hypoxia, AIH) is a novel and exciting intervention that augments mechanisms of neural plasticity. Daily exposure to AIH induces synaptic and cellular plasticity in respiratory motor nuclei and profound recovery of breathing and walking capacity in rats with iSCI. In humans, we found that a single AIH exposure safely enhances ankle torque generation in persons with chronic (>1 year) iSCI. Our most recent study showed that daily AIH (5 consecutive days) was safe and effective in eliciting extended (days) improvement of overground walking speed; combining daily AIH with 30 min of intensive overground walking yielded even greater effects on walking endurance. Thus, daily AIH is a potentially valuable pre-treatment to improve overground walking performance in persons with chronic iSCI.

Despite these exciting findings, important clinical questions remain unanswered. For example, we do not know if more prolonged (weeks) AIH induces longer-lasting locomotor recovery as has been shown in rat models. We hypothesize that prolonged daily exposures (2 consecutive weeks) to modest bouts of low oxygen will enhance more enduring improvements of walking ability in persons with chronic iSCI. Moreover, as ankle torque generation is critical for propulsive force production, and walking speed is positively correlated with propulsive impulse, we anticipate intermittent hypoxia-induced improvements in overground walking ability will likely be due, in part, to AIH-induced increase in ankle torque generation as reported previously. Thus, we also predict that daily exposures to AIH will result in improved fore-aft propulsion forces during overground walking.

Five subjects with chronic iSCI (AIS D; injury onset 8.1±7.0 years) participated in daily AIH followed by 30 min overground walking endurance training (AIH+WALK). Daily AIH+WALK training consisted of 2 consecutive weeks (10 sessions) of 15, 90-second bouts of hypoxia (FIO₂ = 0.09) with 60-sec intervals of normoxia (FIO₂ = 0.21) per training session. We measured walking ability in terms of speed (10-Meter Walk Test) and endurance (6-Minute Walk Test) at baseline (BL), treatment days 5 and 10, and at four follow-ups. We recorded fore-aft ground reaction forces of the more impaired limb at BL, 1- and 4-week follow-up (F1, F4). Blood oxygen saturation, blood pressure, and heart rate were continuously monitored during AIH+WALK. All results were compared with exposure to bouts of normoxia (SHAM)+WALK.

Persistent increases in overground walking were observed in 5/5 subjects following AIH+WALK, but not SHAM+WALK. Mean walking speed and endurance increased from BL to F1 after AIH+WALK (change in speed 0.17 ± 0.04 m/s; endurance 66.6 ± 52.0 m) but not after SHAM+WALK (change in speed 0.01 ± 0.05 m/s; endurance -1.72 ± 52.2 m), with 3 subjects exhibiting walking gains greater than the minimal clinically important difference up to 3.5 weeks post-AIH (F4). Consistent with our hypothesis, 4/4 participants demonstrated increased fore-aft propulsive impulse during overground walking at self-selected speed following AIH+WALK as compared to SHAM+WALK.

Our results offer the first evidence that a prolonged exposure (2 weeks) of mild AIH+WALK may further enhance overground walking speed and endurance due, in part, to increases in fore-aft propulsion. AIH+WALK was well-tolerated, with no autonomic dysreflexia episodes and a low systemic hypertension incidence rate. These results compliment early findings in rat and human locomotor behavior and offer promise for the use of AIH+WALK in walking rehabilitation post-iSCI.
AGE-RELATED DECLINES IN KLOTHO DRIVE DYSFUNCTIONAL MUSCLE PROGENITOR CELL BIOENERGETICS AND IMPAIRED SKELETAL MUSCLE REGENERATION

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Skeletal muscle regenerative capacity declines with increasing age. While young muscle is capable of restoring the original architecture of the damaged myofibers, aged muscle displays increased fibrosis at the expense of regeneration. We show here that expression of the “anti-aging” protein, Klotho, is highly up-regulated within injured skeletal muscle and muscle progenitor cells (MPCs), but that the response to injury is attenuated with aging. Genetic silencing of Klotho in young MPCs drives pathogenic mitochondrial morphology and decreased functional capacity. Conversely, supplementing aged MPCs with Klotho restores mitochondrial bioenergetics to levels approaching young counterparts. <em>In vivo</em>, silencing of the <em>Klotho</em> gene in the muscle of young mice impairs myogenesis and increases fibrosis after injury, thereby confirming the physiological relevance of Klotho in muscle regeneration. These studies identify a novel role for Klotho in the regulation of MPC bioenergetics, and implicate Klotho declines as a driver of impaired muscle regeneration with age.
Short-term effects of real-time gait biofeedback on post-stroke gait biomechanics

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INTRODUCTION: In individuals with post-stroke hemiparesis, reduced push-off force generation in the paretic leg negatively impacts walking function. Gait training interventions that increase paretic propulsion can improve walking function and gait symmetry in individuals with neurologic impairment. A previous study has shown that propulsive biofeedback can increase propulsive force generation bilaterally in older adults. However, it is unknown whether individuals with post-stroke hemiparesis can selectively increase propulsive force generation from the paretic leg in response to unilateral propulsive feedback. The objective of the present study was to determine the short-term effects of a gait training session comprising unilateral propulsive biofeedback on gait biomechanics in individuals with post-stroke hemiparesis.

METHODS: 7 individuals with post-stroke hemiparesis (>6 months post-stroke) participated in one gait training session comprising 18-minutes of treadmill walking with intermittent real-time visual and auditory biofeedback aimed at unilaterally increasing anteriorly-directed ground reaction force in the paretic leg. Ground reaction forces and lower-limb kinematics and kinetics were recorded before training, immediately after training, and during retention tests performed at 15- and 30-minutes post-training.

RESULTS: Subjects significantly increased weight-normalized paretic propulsion by 4±2 %BW compared to pre-training (p<0.0002). Significantly increased paretic propulsion was maintained 30-minutes post-training, demonstrating short-term recall of the gait pattern adopted during biofeedback training. Increased paretic propulsion was accompanied by significant improvements in two key determinants of paretic propulsion: trailing limb angle (increased post-training by 4±3°, p=0.017) and ankle plantarflexor moment (increased post-training by 0.2±0.2 Nm/kg, p=0.025). Ongoing data analysis will evaluate changes in other kinematic and kinetic measures, as well as gait symmetry, during retention tests.

DISCUSSION: This is the first demonstration of short-term improvements in post-stroke gait following unilateral gait biofeedback targeting paretic propulsion. As a rehabilitation tool, real-time biofeedback offers the advantage of providing accurate and immediate knowledge of performance during training, which can enhance motor learning. Future studies will investigate optimum dosing regimens and long-term effects of real-time gait biofeedback training in individuals with post-stroke hemiparesis.
EARLY REHABILITATIVE INTERVENTIONS TO ADDRESS SKELETAL MUSCLE METABOLIC CAPACITY FOLLOWING VOLUMETRIC MUSCLE LOSS INJURY

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Any surgery or severe trauma to the muscle that results in a large-scale loss of muscle tissue is known as a volumetric muscle loss (VML) injury. After VML injury, prolonged inflammation, fibrosis, and poor muscle regeneration can result in long-term muscle dysfunction that may be accompanied by skeletal muscle mitochondrial dysfunction. Rehabilitative interventions that aim to improve the skeletal muscle metabolic capacity post-VML may be a potential means of enhancing functional recovery following VML.

PURPOSE: To determine the extent to which 1, 2, and 4 months of early interventions impact skeletal muscle metabolic capacity following VML.

METHODS: VML was performed on the gastrocnemius and soleus muscles of 8-week old male C57BL/6 mice. Mice were divided into 3 post-VML intervention groups (n=5-6/group). Group 1 (ROM): passive ankle range of motion; Group 2 (ROM-E): passive ankle ROM with the addition of intermittent isometric contractions elicited by electrical stimulation; Group 3 (ROM-E-GPA): ROM-E with the supplementation of 1% β-guanidinopropionic acid (GPA) mixed in standard chow. All groups performed two 30-minute intervention sessions per week. Mice were sacrificed at 1, 2, and 4 months post-VML. Body mass and gastrocnemius muscle masses were recorded at time of sacrifice. A metabolically challenging contractile test was performed on the plantarflexor muscles of the injured limb. Measures of mitochondrial content (i.e. citrate synthase activity) and function (i.e. state 3 mitochondrial respiration rate from permeabilized muscle fibers) were assessed on both the injured and uninjured gastrocnemius muscle fibers.

RESULTS: ROM-E-GPA mice had ~9% and ~13% lower body masses compared to ROM and ROM-E, respectively (P < 0.001). The mass of the injured gastrocnemius muscles were ~24% lower than the uninjured gastrocnemius muscle (P < 0.001). In addition, ROM-E-GPA mice had ~65% and ~38% greater contractile fatigue resistance compared to ROM and ROM-E mice, respectively (P < 0.001). Mitochondrial content (1 month only) and function were not different between uninjured and injured limbs (P = 0.64), and no differences were found across time or treatment conditions (P = 0.77).

CONCLUSION: Preliminary findings suggest that mitochondrial function and content in gastrocnemius muscle fibers were not affected by VML or any post-VML rehabilitative interventions. However, the β-GPA treatment potentially aided in recovery of contractile function as the ROM-E-GPA mice had greater contractile fatigue resistance compared to the ROM and ROM-E groups.
Muscle-contraction training can enhance the efficacy of cell transplantation treatment for Duchenne Muscular Dystrophy (DMD)

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Muscle stem cell transplantation therapy is one of the hopeful therapies for intractable muscular diseases such as Duchenne muscular dystrophy (DMD). In adult skeletal muscles, satellite cells act as a stem cell with regenerating damaged myofibers. We have been investigating generation of muscle stem cells from human iPS cells. Although, a lot of reports showed effects of cell transplantation therapy toward DMD, the best way of cell transplantation into skeletal muscle and valid evaluating method to assess the efficacy of cell therapy have not been developed yet. Therefore we tried to establish the most stable and efficient method of cell transplantation in skeletal muscle by using human immortalized myogenic progenitor cell (Hu5/KD3), and the best way to assess the functional recovery of cell transplanted muscle of DMD model mice (DMD-null/NSG). Moreover, we are also trying to establish an effective rehabilitation programs to promote the effect of cell transplantation therapy toward DMD. These newly developed techniques could be a fundamental steps for establishment of cell therapy towards DMD patients.
Title: Effect of Altered Joint Loading on Cartilage Degeneration, Voluntary Activity, and Knee Kinematics in Rats after Medial Meniscal Transection

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Background: Either reduced or elevated joint loading has been associated with post-traumatic osteoarthritis (OA); however, which altered loading condition may be more detrimental to cartilage health post injury remains unknown. Additionally, the effects of altered joint loading on cartilage degeneration and limb function in rats with medial meniscal transection (MMT)--the most commonly used rodent OA model to test the efficacy of interventions--has not been determined. Purpose: To establish the effects of reduced and elevated joint loading on cartilage degeneration, knee kinematics during locomotion, and degree of voluntary activity in rats post-MMT. Methods: A total of 22 adult male Lewis rats receiving MMT in their left hind limbs were assigned to one of the following three conditions: 1) regular loading (N = 7, 296 ± 56 gm), 2) reduced loading via hind-limb immobilization (N=8, 296 ± 57gm), and 3) elevated loading via daily treadmill running (N = 7, 290 ± 52 gm). A sham surgery was also performed in 7 adult male rats (335 ± 53 gm). All rats were evaluated pre-MMT and at 2, 5, and 8 weeks post-MMT for the amount of voluntary daily run time and distance on a wheel and hind-limb joint kinematics during treadmill locomotion using 3D high-speed X-ray motion analysis. Rats were euthanized at the end of the 8th week. The 3D microstructure and composition of the tibial plateau cartilage and subchondral bone was quantified using contrast enhanced microcomputed tomography (i.e., EPIC-µCT). Results: On average, the reduced-loading group demonstrated a greater reduction in voluntary daily wheel run time and distance than the regular- and elevated-loading groups at the 2nd and 5th week post-MMT (P < 0.05). The reduced-loading group also had a greater reduction in voluntary run time and distance than the elevated-loading group at the 8th week post-MMT (P < 0.05). Based on preliminary data from 1-2 rats per group, the greatest degree of OA (i.e., lesion volume and exposed bone area) was observed in the elevated-loading rats, followed by the regular-loading rats. All three MMT groups demonstrated a more extended knee position (by about 10-15°) at mid-stance during locomotion when compared to the sham rats. Conclusions: Data analysis is currently underway. Our preliminary findings suggest that while elevating joint loading (via treadmill running) facilitated post-traumatic OA, reducing joint loading (via immobilization) may delay OA progression in MMT rats. However, the difference in cartilage degeneration among different loading conditions may not correlate with the behavior changes in voluntary activity and knee locomotion kinematics. Establishing the effects of altered joint loading on cartilage health and limb function in this specific rodent OA model is essential for assessing the effects of rehabilitation on the efficacy of regenerative therapies (e.g., stem cell treatment) that are thought to be sensitive to joint loading environment.