Regenerative Rehabilitation Symposium Course # 5396
Doubletree by Hilton at Mayo Clinic, Rochester, MN 59904
September 24-2015

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Organized by:

University of Pittsburgh School of Medicine
Center for Continuing Education in the Health Sciences
The purpose of the Center for Continuing Education in the Health Sciences is to advance the academic, clinical, and service missions of the University of Pittsburgh Schools of the Health Sciences and the University of Pittsburgh Medical Center through the continuing professional development of physicians, pharmacists, and other health professionals and the translation of biomedical knowledge into clinical practice.

https://ccehs.upmc.com/

UPMC Rehabilitation Institute
The largest rehabilitation provider in Western Pennsylvania, the UPMC Rehabilitation Institute (RI) serves as the hub of a UPMC network of more the 70 rehabilitation facilities that combine clinical care and research to help patients regain independence and enhance their quality of life. The RI's academic partners include the Department of Physical Medicine and Rehabilitation at the University of Pittsburgh School of Medicine and the School of Health and Rehabilitation Science. These academic partners are national and international leaders in rehabilitation research and education.

http://www.upmc.com/Services/rehab/rehab-instiute/Pages/default.aspx

The McGowan Institute for Regenerative Medicine
The McGowan Institute for Regenerative Medicine is a partnership between the University of Pittsburgh and UPMC, and serves as a base for scientists and clinical faculty working in tissue engineering and biomaterials, cellular therapies, and medical devices and artificial organs. McGowan's mission is the development of innovation clinical protocols and the commercial transfer of new technologies.

http://www.mcgowan.pitt.edu

University of Pittsburgh School of Health and Rehabilitation Sciences
Through academic research, technology design and rigorous training, the School of Health and Rehabilitation Sciences (SHRS) at the University of Pittsburgh educates the next generation of health professionals who will help others reach their fullest potential.

At SHRS, we are committed to providing the best learning experience and academic environment possible for our students. Instructional excellence is rigorously pursued. Class sizes are intimate, fostering intellectual exchange and discourse. Students are challenged to not just achieve but to excel. And they do. Graduates of SHRS programs are some of the most sought-after professionals.

Our faculty is world class. They are authors, clinicians, noted researchers, speakers and consultants. But foremost, they are teachers… Teachers who care passionately about their field and about their students. They want their students to succeed in the classroom and in their chosen professions.

An SHRS education is more than classroom lectures. It's hands-on learning either in a clinical setting or in the community. Through our strong relationships with the University of Pittsburgh Medical Center and other clinical partners, our students benefit from a wealth of experiences related to their particular field and area of interest. Students train in schools, hospitals, skilled nursing facilities, ambulatory care sites, and in home and community based settings.

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- Clinical Dietetics and Nutrition
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- Rehabilitation Science (undergraduate)
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University of Pittsburgh Department of Physical Medicine and Rehabilitation

Advancing the Science and Practice of Rehabilitation Medicine

Our mission is to maximize the health, function and well-being of the people and populations we serve by providing the highest quality rehabilitative medical care, conducting highly relevant, cutting-edge research, and training the next generation of clinicians and researchers.

Our research portfolio includes:

- Neural Engineering and Neural Prosthetics
- Biologics as indicators of pain, injury and recovery
- Axon Regeneration
- Biomarkers for brain injury
- Medical homes for Spinal Cord Injury Care
- Motor learning using Transcranial Magnetic Stimulation

Our physicians are experts in the fields of traumatic brain injury, spinal cord injury, sports and musculoskeletal medicine, pain medicine, stroke and many conditions that would benefit from rehabilitation care. We partner with patients to design and implement personalized approaches that maximize participation, recovery and well-being.

http://www.rehabmedicine.pitt.edu/

Rehabilitation Research and Development Program at the Veterans Affairs Palo Alto Health Care System, Center for Tissue Repair, Regeneration, and Restoration

Dr. Thomas Rando directs the Rehabilitation R&D program at the Palo Alto VA. Within that program, the "Center for Tissue Repair, Regeneration, and Restoration" (CTR3) focuses primarily on the neuromuscular and musculoskeletal systems and pursues research at the levels of stem cell biology, biomedical engineering, and clinical / translational research.

The VA Palo Alto Rehabilitation R & D Program reflects a long-standing commitment by the Department of Veterans Affairs to advance the well-being of American veterans through support of a full spectrum of rehabilitation research, from concept to clinic.

A firm scientific understanding of the underlying impairment and a multi-disciplinary team creates a strong basis for developing new clinical treatments that reduce the disability of veterans and improve the effectiveness of healthcare delivery by VA clinicians.

A Special Thanks to…….

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Reducing the burden of neurological disease...

Course Overview and Objectives:

Overview

Medical advances in the field of Regenerative Medicine are accelerating at an unprecedented rate. Regrowing a lost limb, restoring function to a diseased organ, or harnessing the body's natural ability to heal itself are becoming part of our reality instead of a distant promise. Technologies, such as cellular therapies, bioscaffolds, and artificial devices, are now in use or are being tested in clinical trials throughout the country.

- How do we as clinicians and rehabilitation professional work with the patient regenerative medicine team to maximize patient outcomes and to help fully translate research?

- How do we as investigators in the field of regenerative medicine make the most of these revolutionary results?

Few opportunities are available to bring together scientists and clinicians working in these two currently quite disparate fields: rehabilitation science and regenerative medicine. However rehabilitation science and regenerative therapies have to work closely in order to achieve a successful outcome for the patient. This situation created the need for open cross disciplinary work and collaborative communication. This symposium provides the opportunity for researchers and clinicians from around the world to gather and learn about the latest developments, share ideas and concepts and create sustainable collaborations.

Objectives

During this course, participants will:

- Interact with cutting-edge researchers.
- Learn of the status of translating scientific discoveries into clinical practice.
- Network with colleagues and potential collaborators.
- Raise questions, debate implications, plan follow-up studies, and discuss results.
- Share the status of their own research and clinical observations.
- Meet with presenters to learn about their thinking and future research directions.

Continuing Education Credit

Pennsylvania:

University of Pittsburgh's Center for Continuing Education in the Health Sciences:

The University of Pittsburgh School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The University of Pittsburgh School of Medicine designates this live activity for a maximum of 11.75 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Other health care professionals are awarded 1.1 continuing education units (CEU's) which are equal to 11.75 contact hours.

Continuing Education Units

The University of Pittsburgh, School of Health and Rehabilitation Sciences is a pre-approved provider for the State Board of Physical Therapy in Pennsylvania. They have designated this educational activity for a maximum 12 general CEUs.

The University of Pittsburgh is an affirmative action, equal opportunity institution.

Minnesota:

This course meets the criteria for up to 12 hours category I Continuing Education Units per Minnesota Physical Therapy Rules 5601.2400

PROGRAM AGENDA

THURS, SEPT 24TH		**LOCATION**
1:30-6:30pm	Registration Open at Doubletree outside of University Halls	**Atrium-2nd Floor**
2:30-3:30	Pre-Symposium Workshop: "*Regenerative Medicine 101*" **Fabrisia Ambrosio, PhD, MPT,** Assistant Professor, University of Pittsburgh	**Doubletree:** University Hall II-IV
5:30-7:00pm	Registration Open at Geffen Auditorium	Geffen Auditorium, Gonda Bldg.
6:00pm	**Opening of Symposium:**	
6:00-7:30	*Plenary session - "Pathway to the clinic: Translational examples of regenerative rehabilitation for the treatment of volumetric muscle injuries"*	**Mayo Clinic Campus:**
6:00-6:10	Welcome and Introductions: Moderator: **Michael Boninger, MD**, Professor and Chair of Physical Medicine and Rehabilitation, University of Pittsburgh; Medical Director of the Center of Excellence in Wheelchairs and Associated Rehabilitation Engineering at the VA Pittsburgh Health Care System.	Geffen Auditorium, Gonda Bldg.
6:10-6:35	**Thomas Rando, MD, PhD,** Chief of Neurology and Director, Rehabilitation Research & Development, VAPAHCS and Professor of Neurology and Neurological Sciences, and Director of the Glenn Center for the Biology of Aging, Stanford University School of Medicine Title: **"Enhancing Stem Cell Therapeutics for Volumetric Muscle Loss"**	
6:35-7:00	**Benjamin T. Corona, PhD,** Research Physiologist, Extremity Trauma and Regenerative Medicine, Center for the Intrepid, San Antonio Military Medicine Center, San Antonio, TX Title: **"Teaching an Old Dog New Tricks: An Autologous Muscle Tissue-based Therapy for Regenerative Rehabilitation of Volumetric Muscle Loss Injury"**	
7:00-7:25	**Stephen Badylak, DVM, PhD, MD,** Professor of Surgery, and Deputy Director of the McGowan Institute for Regenerative Medicine at the University of Pittsburgh Title: **"Clinical Translation Strategies for Functional Skeletal Muscle Reconstruction"**	
7:25-7:30	Wrap-up and conclusion of day one	
7:30-8:30	*Evening cocktail reception*	Landow Atrium, Gonda Bldg.
FRIDAY, SEPT 25TH		**DOUBLETREE**
7:00am	Registration Opens at Doubletree outside of University Hall	**Atrium-2nd Floor**
7:15-8:15	Continental Breakfast *Seating in University Hall I, Commons and Boardrooms A & B*	Atrium-2nd Floor
8:00-8:15	*Introductory Remarks by:* **Fabrisia Ambrosio PhD, MPT,** Assistant Professor, University of Pittsburgh *Introduction of Keynote Speaker:*	University Hall II-IV

	Thomas Rando, MD, PhD, Chief of Neurology and Director, Rehabilitation Research & Development, VAPAHCS and Professor of Neurology and Neurological Sciences, and Director of the Glenn Center for the Biology of Aging, Stanford University School of Medicine	
8:15-9:15	***Keynote:*** **Tony Wyss-Coray, PhD,** Professor of Neurology and Neurological Sciences, Stanford University and co-Director, Stanford Alzheimer's Disease Research Center and Associate Director, Center for Tissue Regeneration, Repair and Restoration, Palo Alto VA Title: **"Systemic Regulation of Brain Aging and Plasticity"**	University Hall II-IV
Session #1: Interfacing Rehabilitation with Gene Therapies Moderated by: **Carmen Terzic, MD, PhD,** Chair of Physical Medicine and Rehabilitation, Mayo Clinic		
9:15-9:40	**Andre Terzic, MD, PhD,** Director, Mayo Clinic Center for Regenerative Medicine Title: **"Regenerative Medicine Blueprint: From Principles to Practice"**	University Hall II-IV
9:40-10:05	**Martin Childers, DO, PhD,** Professor of Rehabilitation Medicine, University of Washington Title: **"Gene Therapy for Neuromuscular Diseases. Surprising Lessons Learned from Dogs"**	University Hall II-IV
10:05-10:20	*Break*	Atrium-2nd Floor
10:20-10:45	**Christopher H. Evans, PhD,** Professor of Orthopedics and Physical Medicine and Rehabilitation, Mayo Clinic Title: **"Gene Therapy for Cartilage and Bone Regeneration"**	University Hall II-IV
10:45-10:55	**M. Terry Loghmani, PT, PhD, MTC**, Associate Professor, Applied Regenerative Medicine Lab, Department of Physical Therapy, Indiana University, School of Health and Rehabilitation Sciences Title: **"Instrument-Assisted Soft Tissue Mobilization in Healthy Young Adult Males Mobilizes Tissue-Resident Mesenchymal Stem Cells into Circulation"**	University Hall II-IV
Session #2: Mechanical Stimulation as a Tool to Promote Musculoskeletal Regeneration Moderated by: **Linda Noble-Haeusslein, PhD,** Professor of Neurological Surgery and Physical Therapy and Rehabilitation, University of California, San Francisco		
10:55-11:20	**Nathan LeBrasseur, PhD,** Associate Professor and co-chair of Research, Physical Medicine and Rehabilitation, Mayo Clinic Title: **"The Effect of Exercise on Skeletal Muscle Signaling Responses"**	University Hall II-IV
11:20-11:45	**George J. Christ, PhD,** Professor of BME and Orthopaedic Surgery and Director of Basic Science & Translational Research for Orthopaedic Surgery, University of Virginia Title: **"Development of a Tissue Engineered Muscle Repair Technology Platform for Treatment of Volumetric Muscle Loss Injuries"**	University Hall II-IV
11:45-12:10	**Fabrisia Ambrosio PhD, MPT,** Assistant Professor, University of Pittsburgh Title: **"Electrical Stimulation Rejuvenates Muscle Stem Cell Behavior"**	University Hall II-IV

12:10-12:20	**Karina Nakayama, PhD,** Postdoctoral Fellow, Huang Lab, Cardiovascular Institute, Stanford University Title: **"Engineering Vascularized Skeletal Muscle with Physiologically-Relevant Cellular Organization"**	University Hall II-IV
12:20-12:30	**Nana Takenaka-Ninagawa, PhD,** Postdoctoral Fellow, Japan Society for the Promotion of Science, Center for iPS Cell Research and Application, Kyoto University, Kyoto, Japan Title: **"Study of Cell Transplantation Method Towards the Skeletal Muscle Regeneration"**	University Hall II-IV
12:30-1:30 12:30-1:30 12:30-2:30	*Buffet Lunch** *Meet the Mentor [check with registration for details]* *Poster Session & Networking* *[Poster Presenters are to be at their posters between 1:30 and 2:30pm]* **Seating in University Hall I, Commons Room & Boardroom I & II*	Atrium-2nd Floor Commons Room Chancellor Room
2:30 – 3:05	Panel Discussion on '***Regenerative Rehabilitation from the educators and students perspectives'*** Moderators: **Anthony Delitto, PhD, PT, FAPTA**, Professor and Interim Dean, School of Health and Rehabilitation Sciences, University of Pittsburgh and **Kimberly Topp, PhD, PT,** Professor and Chair of the Department of Physical Therapy and Rehabilitation Sciences, University of California, San Francisco Panelists: **Matthew Muchnick**, DPT student, Widener University **Junichi Tajino, PhD**, Post-doctoral fellow, Kyoto University, Kyoto, Japan **Carolina Onodera**, PhD student, UNICAMP (Universidade Estadual de Campinas), Campinas, Brazil	University Hall II-IV
Session #3: Manipulation of the Microenvironment to Enhance Neurological Regeneration and Recovery Moderated by: **Fabrisia Ambrosio, PhD, MPT,** Assistant Professor, University of Pittsburgh		
3:05-3:30	**Linda Noble-Haeusslein, PhD,** Professor of Neurological Surgery and Physical Therapy and Rehabilitation, University of California, San Francisco Title: **"Brain-derived Stem Cells as a Strategy to Reduce Bladder Dysfunction and Neuropathic Pain After Spinal Cord Injury"**	University Hall II-IV
3:30-3:55	**Randy Trumbower, PT, PhD,** Assistant Professor of Rehabilitation Medicine, Emory University Title: **"Acute Intermittent Hypoxia: A Breath-taking Approach to Enhance Motor Recovery After Spinal Injury"**	University Hall II-IV
3:55-4:10	*Break*	Atrium-2nd Floor
4:10-4:35	**Kendall H. Lee, MD, PhD,** Professor of Neurosurgery and Physiology**,** Mayo Clinic And **Peter Grahn,** Neural Engineering Lab, Department of Neurosurgery, Mayo Clinic Title: **"Limb Reanimation After Spinal Cord Injury"**	University Hall II-IV

4:35-4:45	**Andrew D. Kleven, DPT,** Mayo Clinic School of Health Sciences, Department of Physical Medicine and Rehabilitation, Rehabilitation Medicine Research Center, Mayo Clinic Title: **"Interactions between Exercise Training and Dietary Fat Modulate Myelinogensis in the Adult Spinal Cord"**	University Hall II-IV
4:45-5:45	Town Hall / Panel Discussion: ***'Defining Compatibility Gaps and Programmatic Needs: Department of Defense, Veterans Affairs and National Institute of Health Perspectives'*** Moderator: **Thomas Rando, MD, PhD,** Chief of Neurology and Director, Rehabilitation Research & Development, VAPAHCS and Professor of Neurology and Neurological Sciences, and Director of the Glenn Center for the Biology of Aging, Stanford University School of Medicine Panelists: **Tim Brindle, PhD**, Scientific Program Manager, US Department of Veterans Affairs **Christopher L. Dearth, PhD,** Facility Research Director – EACE, WRNMMC, Director of Research – DoR, WRNMMC, Assistant Professor, PM&R, USUHS **Ralph Nitkin, PhD**, Program Director, Biological Sciences and Career Development, NCMRR, NICHD, NIH	University Hall II-IV
5:45 – 5:50	*Wrap-up for the day* **Fabrisia Ambrosio PhD, MPT,** Assistant Professor, University of Pittsburgh	
6:00-8:00	*Reception & Tours of Mayo campus facilities*	Mayo Clinic: Dan Abraham Healthy Living Center (DAHLC)
SATURDAY, SEPT 26TH		**DOUBLETREE**
7:15-8:15	Continental Breakfast	Atrium-2nd Floor
8:00-9:00	***"Global perspectives in Regenerative Rehabilitation"*** Moderator: **Michael Boninger, MD,** Professor and Chair of Physical Medicine and Rehabilitation, University of Pittsburgh; Medical Director of the Center of Excellence in Wheelchairs and Associated Rehabilitation Engineering at the VA Pittsburgh Health Care System Panelists: **Hong Chen, MD, PhD**, Associate Professor, Department of Rehabilitation, Stem Cell Research Center of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China **Carmelo Chisari, MD,** Chief of the Laboratory, University Hospital of Pisa, Pisa Italy **Hiroshi Kuroki, PhD, RPT**, Professor, Motor Function Analysis, Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan **Akira Ito, PT, PhD,** Postdoctoral fellow of Japan Society for the Promotion of Science (JSPS), Department of Orthopaedic surgery, Graduate School of Medicine, Kyoto University **Fabrisia Ambrosio, PhD, MPT,** Assistant Professor, University of Pittsburgh	University Hall II-IV

9:00-10:00	***Local Keynote:*** **Anthony J. Windebank, MD***, Professor of Neurology, Mayo Clinic* Title: **"Regenerative Medicine in the Nervous System"**	University Hall II-IV
Session #4: Interfacing Rehabilitation with Stem Cell Therapies Moderated by: **Michael Boninger, MD,** Professor and Chair of Physical Medicine and Rehabilitation, University of Pittsburgh; Medical Director of the Center of Excellence in Wheelchairs and Associated Rehabilitation Engineering at the VA Pittsburgh Health Care System		
10:00-10:25	**George H. Kraft, MD,** Professor of Rehabilitation Medicine and Neurology, University of Washington Title: **"The Use of Autologous Stem Cells in the Rehabilitation of Multiple Sclerosis"**	University Hall II-IV
10:25-10:35	**Break**	Atrium-2nd Floor
10:35-10:00	**Marni D. Boppart, Sc.D.,** Associate Professor of Kinesiology and Community Health, University of Illinois Title: **"Stem Cell Transplantation & Exercise for Muscle Regeneration"**	University Hall II-IV
11:00-11:25	**Carmen Terzic, MD, PhD,** Chair of Physical Medicine and Rehabilitation, Mayo Clinic Title: **"Stem Cell Therapies and Cardiovascular Rehabilitation"**	University Hall II-IV
11:25-11:35	*Closing remarks:* **Fabrisia Ambrosio PhD, MPT,** Assistant Professor, University of Pittsburgh *Announcement on the 5th Symposium:* **Randy Trumbower, PT, PhD,** Assistant Professor of Rehabilitation Medicine, Emory University	University Hall II-IV

Presenter information:

Speakers:

Fabrisia Ambrosio, PhD, MPT graduated with a Master of Science in Physiology-Endocrinology from Laval University in Québec City, Québec and a Master of Physical Therapy from the Medical College of Pennsylvania and Hahnemann University. In 2005, Dr. Ambrosio graduated with a PhD in Rehabilitation Science & Technology from the University of Pittsburgh. Also in 2005, she accepted a position as a faculty member in the Department of Physical Medicine & Rehabilitation at the University of Pittsburgh. She holds secondary appointments in the Departments of Physical Therapy, Orthopaedic Surgery, and Microbiology & Molecular Genetics at the University of Pittsburgh, and is a faculty member of the McGowan Institute for Regenerative Medicine.

Dr. Ambrosio's research has the long-term goal of developing regenerative rehabilitation approaches to improve the skeletal muscle healing and functional recovery. Her laboratory investigates the underlying mechanisms by which targeted and specific mechanotransductive signals can be used to enhance donor and/or endogenous stem cell function using mouse and human models.

Presentation abstract:
In older adults, muscle trauma resulting from an injury or surgery may initiate a devastating cascade of functional declines; a cascade that is, at least partially, attributed to failed muscle healing. Muscle regeneration is predominantly dictated by the action of muscle stem, or "satellite", cells (MuSCs), a reserve cell population that demonstrates considerable dysfunction with increasing age. According to the stem cell niche concept, stem cell responses are significantly influenced by biophysical and biochemical cues that emanate from the surrounding microenvironment. While it is evident that MuSC activation, self-renewal, proliferation and differentiation are regulated by physical and dynamic niche interactions, a mechanistic understanding of the effect of age-related alterations in skeletal muscle mechanical properties on MuSC behavior and regenerative potential has been lacking.

In Dr. Ambrosio's presentation, she will share her work investigating mechanisms underlying the decline in muscle regenerative capacity over time, and the potential for the application of targeted mechanical stimulation protocols to rejuvenate skeletal muscle healing in an aged population.

Stephen Badylak, DVM, PhD, MD is a Professor in the Department of Surgery, and deputy director of the McGowan Institute for Regenerative Medicine at the University of Pittsburgh.

Dr. Badylak has practiced both veterinary and human medicine, and is now fully engaged in research. Dr. Badylak began his academic career at Purdue University in 1983, and subsequently held a variety of positions including service as the Director of the Hillenbrand Biomedical Engineering Center from 1995-1998.

Dr. Badylak holds over 50 U.S. patents, 200 patents worldwide, has authored more than 300 scientific publications and 40 book chapters. He has served as the Chair of several study sections at the National Institutes of Health (NIH), and is currently a member of the College of Scientific Reviewers for NIH. Dr. Badylak has either chaired or been a member of the Scientific Advisory Board to several major medical

device companies. More than four million patients have been treated with bioscaffolds developed in Dr. Badylak's laboratory.

Dr. Badylak is a Fellow of the American Institute for Medical and Biological Engineering, a member of the Society for Biomaterials, a charter member of the Tissue Engineering Society International, the immediate past president of the Tissue Engineering Regenerative Medicine International Society (TERMIS) and a Founding International Fellow of TERMIS.

Dr. Badylak's major research interests include:

- Naturally Occurring Biomaterials, including Extracellular Matrix, and Biomaterial/Tissue interactions
- Developmental Biology and its Relationship to Regenerative Medicine
- Relationship of the Innate Immune Response to Tissue Regeneration
- Biomedical Engineering as it Relates to Device Development and Biomaterials
- Clinical Translation of Regenerative Medicine

Presentation abstract:

Clinical investigations of the application of extracellular matrix scaffolds and the implementation of physical therapeutics as of means of maximizing functional recovery after VML.

Background: Cell-based strategies, scaffold-based strategies, and / or bioactive molecule-based approaches for functional skeletal muscle reconstruction following Volumetric Muscle Loss [VML] have been attempted with varying degrees of success. By far, cell-based strategies dominate the therapeutic landscape, but meaningful functional improvements by this approach following VML have been disappointing. A variety of stem/progenitor cell approaches have been investigated, all of which are plagued by the problem of minimal cell survival in the early transplantation period. Paracrine effects have been proposed as an explanation for any documented incremental changes. In addition, cell-based approaches are challenged by significant regulatory and reimbursement hurdles. Bioactive molecules, including gene therapy approaches, have been marginal success when confronted with VML. Such approaches have been more effective for less severe injuries. The use of scaffold materials has shown the greatest amount of promise, especially approaches with acellular matrix-based scaffolds. The bioactivty associated with naturally occurring ECM-based scaffolds includes modulation of the innate immune response and recruitment of endogenous stem cells.

It is likely that future strategies will include combinations of the above approaches and patient-specific factors are likely to play a significant role in identification of the most appropriate approach. The inclusion of aggressive rehabilitation following any of the above approaches has been given minimal attention, but represents as important variable to consider in any potentially effective strategies.

Marni Boppart, Sc.D., FACSM, received her doctoral degree in Applied Anatomy and Physiology from Boston University, completing the research requirement for her degree at the Joslin Diabetes Center, Harvard Medical School. She is currently an Associate Professor and is the head of the Molecular Muscle Physiology Laboratory, located at the Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign. Her affiliations include the Institute for Genomic Biology (IGB), the Center on Health, Aging, and Disability (CHAD), and the Center for Nutrition, Learning and Memory (CNLM). Her current research is funded by NIH and Abbott Nutrition and focuses on

understanding the cellular and molecular basis for skeletal muscle adaptation in response to exercise, as well as development of novel therapeutics that have the potential to prevent or treat age-related disability.

Presentation Abstract:
Satellite cells reside in adult skeletal muscle for the purpose of myofiber repair and regeneration following injury. Elucidation of the intrinsic and extrinsic factors that influence satellite cell activation and differentiation is necessary for identification of strategies to preserve and/or treat aged, diseased or severely injured skeletal muscle. Recent studies suggest that mononuclear stem cells with multilineage potential, including mesenchymal stem cells (MSCs), are present in skeletal muscle that directly or indirectly enhance capacity for repair and/or regeneration. Our data suggest that MSCs isolated from skeletal muscle release important growth factors in response to mechanical strain that facilitate satellite cell proliferation, and that transplantation of MSCs preconditioned with mechanical strain positively impact multiple tissues in aged mice. This information suggests that MSC paracrine factor release may provide the basis for improvements in muscle structure and function with physical rehabilitation.

Martin K. (Casey) Childers, DO, PhD, Professor, Department of Rehabilitation Medicine and Investigator at the Institute for Stem Cell & Regenerative Medicine, University of Washington. Graduate of Seattle Pacific University (B.A., Music Performance), Western University (D.O., Medicine, Osteopathic) and The University of Missouri (Ph.D., Physiology & Pharmacology)

The Childers' laboratory works in two areas of investigation. In collaboration with the French biotechnology institute, Genéthon, work on gene replacement therapy for patients with a rare and deadly muscle disease began with case report in 2008, where a 5-month-old Labrador retriever was reported in a Canadian veterinary medical journal. The dog presented with severe muscle weakness. Further analysis indicated that the dog was affected with a rare disease, termed “Labrador myopathy”. Through the tireless efforts of the mother of a child affected with a rare – and analogous- disease, termed myotubular myopathy, the Childers research group was able to acquire a first-degree relative, a dog named “Nibs”, a Labrador retriever coming from a line of dogs with a history suspicious for the rare disease. It was later discovered that Nibs harbored a canine gene mutation, the same gene known to cause myotubular myopathy in patients. Through patient donations, a canine research colony was started. Dogs in this colony later provided the “proof-of-principle” that gene replacement worked to “cure” affected dogs, but the treatment worked far better than previously thought possible. Based on this unexpected and groundbreaking discovery, the biotech company, Audentes Therapeutics, was founded in 2012 dedicated to bring gene therapy to the first human myotubular myopathy clinical trial.

In 2012, a graduate student in the Childers lab discovered that cells found in the urine of a patient with Duchenne muscular dystrophy (DMD) could be collected, expanded in a petri dish, an “reprogrammed” to form beating human heart cells. This discovery was important, because for DMD patients, the ultimate cause of death is heart failure. The student’s discovery led the group to develop tests that could be adapted for drug discovery. The first experiment at the High Throughput Core facility at ISCRM, was recently completed using this "disease in a dish" approach. Millions of beating heart cells reprogrammed from the urine of a patient with Duchenne muscular dystrophy were grown in culture, and later screened against 2000 compounds and FDA approved drugs. This “disease-in-a-dish” screening approach discovered ~40 compounds and drugs that enhanced the survival of DMD heart cells. Ongoing work will identify the most promising new compounds for further development.

Presentation Abstract:

The emerging multidisciplinary field of regenerative medicine aims to develop new technology to repair and replace cells, tissues and organs. Regenerative medicine holds the promise of regenerating damaged tissues and organs in the body by either replacing damaged tissue or by stimulating the body's own repair mechanisms to heal previously irreparable tissues or organs. Regenerative approaches address the root cause of disease and offer prospects of tissue repair previously unthinkable. For degenerative muscular disorders, most fall into the category of rare inherited diseases. To cure inherited muscular disorders, recent attention has focused on the transfer of normal genes to correct mutant diseased genes.

Gene therapy - the process of introducing foreign genomic materials into host cells to elicit therapeutic benefit - became available for clinical practice on November 2, 2012, when Glybera (alipogene tiparvovec) became the first gene therapy in the Western world to receive market approval for patients with lipoprotein lipase (LPL) deficiency, a rare genetic disease previously without effective treatment. Since 1989, gene therapy clinical trials have been undertaken in 31 countries with more than 1800 human trials ongoing, completed or approved worldwide.

Most gene therapy clinical trials have targeted genes involved in cancer with fewer trials initiated in monogenic diseases, such as Duchenne muscular dystrophy (DMD). Therapeutic approaches at replacing defective genes in monogenic diseases of muscle, like DMD, include the use of recombinant viral vectors engineered to target specific tissues. In the 1960s, the discovery of naturally occurring adeno-associated virus (AAV) isolates led to the clinical application of recombinant AAV vectors with early successes in clinical trials. AAV vectors are attractive for clinical use because AAVs are not associated with human disease, the virus persists in the infected host for years and a large “toolkit” of AAV vectors is available as clinical gene therapy delivery tools.

For eventual gene therapy of patients with X-linked myotubular myopathy (XLMTM), our goal was to use a predictive large animal model (the XLMTM dog) to refine the delivery system, to assess critical safety parameters such as the potential host immune response to vector and transgene, and to optimize efficacy measurements. In collaboration with the French non-profit institute, Généthon, cohorts of Mtm1 knockout mice were first tested for response to systemic Mtm1 gene replacement via tail vein injection. Results indicated that a single systemic treatment with AAV-Mtm1 sufficed for long-term (at least one year) survival and essentially complete amelioration of symptoms of mice with myotubularin-deficient muscles. Using the same AAV vectors produced by Généthon scientists and tested in mice, our collaborative research group confirmed that local gene replacement therapy, delivered intramuscularly into the hind limb of young XLMTM dogs, reversed pathological changes in myotubularin-deficient skeletal muscles. Remarkably, the treated muscles also showed nearly normal strength at six weeks post-injection, compared to very weak muscles (only 20 percent of normal strength) in saline-injected contralateral limbs. In subsequent experiments, intravascular administration of AAV8-MTM1 at the same dose used in mice was well tolerated in dogs, rescued the skeletal muscle pathology and respiratory function, and prolonged life for over one year. Together these initial studies demonstrated the feasibility, safety and efficacy of gene therapy with AAV for long-term correction of muscle pathology and weakness observed in myotubularin-deficient mouse and dog models, and support clinical trials aimed at correcting this devastating disease in patients.

George J. Christ, PhD, Professor of BME and Orthopaedic Surgery, Mary Muilenbrrg Stamp Professor of Orthopaedic Surgery, and Director of Basic Science & Translational Research for Orthopaedic Surgery, University of Virginia. Dr. Christ is the Past Chairman of the Division of Systems and Integrative Pharmacology of the American Society of Pharmacology and Experimental Therapeutics (ASPET), and Past President of the North Carolina Tissue Engineering and Regenerative Medicine (NCTERM) group. He is on the Editorial Board of five journals and is an ad-hoc reviewer for 2 dozen others. Dr. Christ has authored 214 scientific publications and is co-editor of a book on integrative smooth muscle physiology and another on regenerative pharmacology. Dr. Christ has served on both national and international committees related to his expertise in muscle physiology, and on NIH study sections in the NIDDK, NICHD, NCRR and NHLBI. He has chaired working groups for both the NIH and the World Health Organization. Dr. Christ is a co-inventor on more than 26 patents (national and international) that are either issued or pending, related to gene therapy for the treatment of human smooth muscle disorders and tissue engineering technologies. Dr. Christ has also been the driving scientific force behind the preclinical studies and IND approvals supporting three Phase I clinical trials for gene therapy for benign human smooth muscle disorders. He is also spearheading the development of a tissue engineered muscle repair (TEMR) technology platform for the treatment of Wounded Warriors, as part of the AFIRM consortium. An IND for a first-in-man pilot study will soon be submitted to further develop this technology for treatment of cleft lip. Dr. Christ has been extensively involved in basic and translational studies of regenerative medicine directed toward vessel tissue engineering and bladder regeneration, and most recently, regenerative pharmacology.

Presentation Abstract:
There are a host of extremity and craniofacial injuries, diseases, disorders or malfunctions for which current therapies are inadequate to restore function and / or cosmesis due to lack of viable autologous muscle tissue. Tissue engineering and regenerative medicine approaches have great potential to restore form and function to these otherwise irrecoverable injuries. Since these injuries occur on a spectrum with respect to the magnitude, location and type of muscle affected, it corresponds to intuition that a variety of therapeutic strategies may be required for ensuring functional recovery. This lecture will describe our efforts to develop a tissue engineered muscle repair (TEMR) technology platform, based on cell-seeded, tunable biomaterials combined with mechanical preconditioning in a bioreactor, which could provide adaptable therapeutic strategies for regenerative and repair of diverse muscle injuries.

Benjamin Corona, PhD, is a Research Physiologist in the Extremity Trauma and Regenerative Medicine task area of the United States Army Institute of Surgical Research. He earned his doctorate in Kinesiology at Georgia State University and was a postdoctoral fellow at the Wake Forest Institute for Regenerative Medicine with a concurrent fellowship with the Armed Forces Institute of Regenerative Medicine. Dr. Corona's current research focuses on the pathophysiology of musculoskeletal injuries after severe trauma, with emphasis on understanding the underlying mechanisms of failed regeneration or progressive degeneration and identifying regenerative and rehabilitative strategies to restore musculoskeletal function. Dr. Corona has investigated volumetric muscle loss injury extensively over the last 6 years in preclinical animal models and patients. Dr. Corona's near-term goal is to perform a clinical investigation of an autologous muscle tissue-based therapy for the treatment of volumetric muscle loss injury.

Presentation Abstract:
Volumetric muscle loss [VML] injury is common in civilian and military trauma and can result in disability. Current evidence indicates that severe VML injuries require Regenerative Rehabilitation to achieve maximal functional improvements. Limb dysfunction in patients with VML is attributed to

muscle weakness that results from the frank loss of muscle tissue and pathophysiology of the remaining musculature, and the loss of range of motion due to extensive fibrosis. Standard physical rehabilitation has not resulted in significant functional or strength improvements specifically of the VML-injured musculature. However, innovative assistive devices (e.g. IDEO) and specialized rehabilitation programs (e.g. Return to Run Program) have improved functional outcomes and in some cases resulted in Wounded Warriors returning to active duty. Ongoing clinical studies developing novel physical therapy programs are observing significant strength gains without *de novo* regeneration of muscle, suggesting amelioration of pathophysiology in the remaining musculature. However, the strengths gains made are ultimately limited to the volume of remaining tissue and therefore regenerative therapies are necessary for optimal functional recovery after severe VML.

The majority of preclinical research efforts investigating VML injury are focused on developing therapeutic approaches to promote *de novo* regeneration of the lost muscle tissue. Skeletal muscle has a remarkable capacity to regenerate under conditions in which key elements 9e.g. satellite cells and basal lamina) of the muscle survive the injury and remain *in situ.* Using endogenous regenerative capacity of skeletal muscle, we have investigated an autologous muscle tissue grafting (minced muscle grafts: $1mm^3$ pieces of tissue) therapy as a *near-term* solution for VML injuries. Across rodent and porcine VML models, autologous muscle grafts have restored over 50% of functional deficits within two months post-injury and promote appreciable *de novo* muscle fiber regeneration. However, despite the significant improvements observed with graft therapy there remains a functional deficit. We broadly tested the hypothesis that physical rehabilitation and autologous graft-medicated *de novo* regeneration may synergistically improve muscle strength in a rodent VML model. We observed that combined physical rehabilitation (i.e. wheel running) and regenerative medicine (autologous grafts) improved muscle strength above values observed with either therapy in isolation. We are currently planning a clinical study to investigate a combined autologous graft therapy and physical rehabilitation therapeutic regimen to improve functional outcomes after VML injury.

Christopher Evans is Professor and Director of the Rehabilitation Medicine Research Center at the Mayo Clinic. He is also the Maurice Müller Professor of Orthopaedic Surgery Emeritus at Harvard Medical School, Clinical Professor of Orthopaedic Surgery at Dartmouth Medical School and Adjunct Professor of Bioengineering at Hampton University.

Prof. Evans gained a first class honours degree in genetics and microbiology, followed by a PhD in biochemistry, at University College Swansea. After a period of post-doctoral training in molecular biology at the Free University of Brussels, Belgium, he came to the Department of Orthopaedic Surgery at the University of Pittsburgh Medical School, where he rose through the ranks to become the inaugural Henry Mankin Professor of Orthopaedic Surgery and Professor, Department of Molecular Genetics and Biochemistry. While at the University of Pittsburgh he obtained a MA in the History and Philosophy of Science. In 1994, he was awarded a DSc by the University of Wales. He was made an Honorary Fellow of Swansea University in 2009. Recruited to Harvard Medical School in 1999, Prof. Evans held first the Robert Lovett Chair and then the Maurice Müller Chair of Orthopaedic Surgery. He is the recipient of an honorary MA from Harvard University. He was recruited to Mayo Clinic in 2013.

Prof. Evans's research interests focus on the application of biological therapies, particularly gene therapy, to the treatment of disorders of bones and joints, a field he pioneered. He was Principal Investigator on the world's first arthritis gene therapy clinical trial and is also developing gene therapies for bone healing and cartilage repair. Arthritis gene therapy is presently in advanced, phase III clinical trials. He is co-founder of two biotechnology companies.

Prof. Evans is a Past-President of the Orthopaedic Research Society and is a Fellow of the Royal Society of Chemistry and the Royal College of Pathologists. He is the recipient of both the Kappa Delta and Nicolas Andry Awards for Orthopaedic Research, The Cabaud Award for Sports Medicine Research, The Marshall Urist Award for Excellence in Tissue Regeneration Research, and the Arthur Steindler Award for significant contributions to the understanding of the musculoskeletal system.

Presentation Abstract:
In the context of tissue regeneration, gene therapy is used as a biological delivery system for the encoded gene products RNA or protein. This form of delivery enables local, authentic and potentially regulated synthesis of the products for an extended period of time. In many cases the transferred genes encode growth factors that stimulate the differentiation of progenitor cells into, in this case, chondrocytes or osteoblasts. Examples of such gene products include bone morphogenetic proteins (BMPs), transforming growth factor-beta (TGA-beta), and insulin-like growth factor (IGFs). Gene transfer is also advantageous for the delivery of products, such as transcription factors, with an intra-cellular site of action.

Vectors are used to transfer genes to their target cells. The most efficient transfer vectors are derived from viruses, taking advantage of the natural ability of viruses to transfer their own genes with high efficiency to the cells they infect. To create a vector for gene therapy, the viruses are genetically manipulated to remove sequences that contribute to virulence and to insert therapeutic genes. Viral vectors used in human gene therapy trails have been derived from retroviruses, adenoviruses, adeno-associated viruses and herpes simplex viruses, among others. Non-viral vectors provide an alternative to those derived from viruses. They are considered by many to be safer and less expensive that viral vectors, but are generally much less efficient. For *in vivo* gene delivery, vectors are introduced directly into the body. For *ex vivo* gene delivery, cells are removed from the body and genetically modified extra-corporally before being re-introduced.

Given the low cellularity of cartilage and its lack of progenitor cells, many pre-clinical studies of cartilage regeneration have used *ex vivo* transfer strategies, using a variety of chonodrogenic genes, including BMP, TGF-beta and IGF-1. Phase II clinical trials have been completed using a line of allogeneic chondrocytes that have been infected with a retrovirus that encodes TGF-beta. The cells are implanted into cartilaginous defects within a fibrin gel. The preliminary data from this trial are encouraging. Gene therapy for bone healing is at a pre-clinical stage, but success has been reported in animal models, particularly using transgenes encoding osteogenic BMPs in conjunction with *ex vivo* delivery using mesenchymal stem cells. Our group focuses on developing affordable, expedited techniques that can be delivered at the point of care.

Andrew D Kleven, SPT, Mayo Clinic School of Health Sciences, Department of Physical Medicine and Rehabilitation, Rehabilitation Medicine Research Center, Mayo Clinic. Andrew is a second year student in the Mayo Doctor of Physical Therapy Program and also working in research in the Neural Repair Laboratory of Dr. Isobel Scarisbrick within the Rehabilitation Medicine Research Center. Andrew has had a strong interest in neuroscience since his undergraduate days at St. Olaf College in Northfield, MN. His research interests include the effects of exercise training on nervous system function and in the context of neurorehabilitation.

Proper myelination is crucial for transmission of information and myelination is likely modulated by the interaction between lipid components and axonal activity. Here we test the hypothesis that dietary

saturated fatty acids alone, or in combination with exercise training, can influence myelin homeostasis in the adult spinal cord. To test this hypothesis, 9 week old adult C57BL6/J male mice were fed a diet enriched in fat (60% total fat, 20% from saturated fat) for a period of 7 weeks, provided access to free wheel running for a corresponding period, or provided access to both interventions in combination. We used quantitative Western blot, real time PCR and immunohistochemical approaches to quantify myelin proteins, oligodendrocyte progenitor cells (OPCs), mature oligodendrocytes, associated growth factor systems, and signaling cascades in the lumbosacral spinal cord of mice under these conditions compared to those with a sedentary lifestyle. Results demonstrate that the abundance of the major myelin membrane proteins, proteolipid (PLP) and myelin basic protein (MBP), as well as NG2, a marker for OPCs, were significantly elevated in the spinal cord after 7 weeks of exercise training in combination with high dietary saturated fats. Expression of MBP and PLP RNA, as well that for Myrf1, a transcription factor driving oligodendrocyte differentiation, were also differentially increased with exercise and/or high dietary saturated fats. In conjunction with these findings however, consumption of a high fat diet alone resulted in a reduction in NG2 and Nkx2.2-OPCs present in the spinal cord white matter of adult mice. A parallel decrease in mature CC-1+-oligodendroglia and those labeled for the pan-OPC and oligodendrocyte marker Olig2 was also seen with consumption of high fat in the context of a sedentary lifestyle. Of potential clinical significance, seven weeks of exercise training completely reversed the deleterious effects of a high fat diet on OPC and oligodendrocyte numbers. Exercise and dietary fatty acid-induced changes in myelinogenesis occurred in parallel with increases in the expression of spinal cord IGF-1 and IGF-1 receptor. Parallel increases in phosphorylated-AKT, a signaling intermediate involved in the myelinogenic effects of IGF-1, was also observed in response to consumption of high dietary saturated fat alone or in combination with exercise. Together these data support a model in which exercise in combination with high dietary saturated fatty acids unleashes a promyelination program that supports myelin homeostasis in the adult spinal cord. These results are crucial for the design of rehabilitative programs to enhance CNS function.

Nathan LeBrasseur, PhD, is an Associate Professor and the Co-Chair of Research in the Department of Physical Medicine and Rehabilitation at Mayo Clinic. He received an M.S in Physical Therapy and his Ph.D. in Applied Anatomy and Physiology from Boston University and conducted postdoctoral studies in Molecular Medicine and Integrative Physiology at Boston Medical Center. He is currently Director of the Healthspan Assessment Laboratory in the Robert and Arlene Kogod Center on Aging, Director of the Muscle Performance and Physical Function Core in the Center for Clinical and Translational Science, and Associate Director of the Glenn Laboratories for Senescence Research at Mayo Clinic. Dr. LeBrasseur conducts translational “bench-to-bedside” research to identify ways to improve physical performance, metabolism and resiliency in the face of aging and disease.

Presentation Abstract:

The accumulation of molecular and cellular damage is a hallmark of aging that compromises a tissue's regenerative potential. Exercise has been shown to invoke protective responses against multiple triggers of damage, including telomere erosion, oxidative stress, protein aggregation, and mitochondrial dysfunction. Moreover, we have recently observed that exercise can prevent cellular senescence. These remarkable effects of exercise and their impact of skeletal muscle regeneration will be presented.

Kendall H. Lee, MD, PhD, is the director of the Mayo Clinic Neural Engineering Laboratory and a professor in the Mayo Clinic Department of Neurologic Surgery with joint appointments in the Department of Physiology and Biomedical Engineering and the Department of Physical Medicine and Rehabilitation. He is also a commander in the U.S. Navy Reserve.

Dr. Lee received a B.A. in biology with a philosophy minor at the University of Colorado at Denver, and then attended Yale University Graduate School, where he received an M.Phil. degree, M.D., and Ph.D. in neurobiology. He interned at the Hospital of St. Raphael, Yale University School of Medicine, and completed a residency year in neurology at Harvard Medical School. He completed an internship in general surgery, residency in neurosurgery, and chief residency in neurosurgery at Dartmouth Hitchcock Medical Center.

In clinical practice, Dr. Lee is an expert on neurological disorders. He performs deep brain stimulation surgery to treat Parkinson's disease, Tourette's syndrome, dystonia, and several other neurodegenerative and psychiatric diseases. He has led his laboratory in the development of several new medical devices to record electrochemical and electrophysiological reactions in the brain to deep brain stimulation.

Dr. Lee's research is funded by multiple grants from the National Institutes of Health and generous private donor funding. His work has been published in peer-reviewed journals including the Proceedings of the National Academy of Sciences, Neuron, Journal of Neural Engineering, Epilepsia, Movement Disorders, Journal of Neurosurgery, and Archives of Neurology. He also serves on the editorial boards for Neurosurgery, the Journal of Neural Engineering, Biomedical Engineering Letters, Stereotactic and Functional Neurosurgery, and Neuromodulation.

Co-presenter:

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I am a fourth-year Ph.D. student at Mayo Clinic in Rochester Minnesota. I have lived my entire life in Minnesota, growing up on a small dairy farm near the town of Willmar. In 2005 I suffered a severe swimming accident that resulted in a cervical spinal cord injury (SCI) and permanent paralysis. In the days and months following my injury, I was left with limited therapeutic options and a poor prognosis for regaining the function I had lost. My prognosis was bleak, however, I was fascinated with how little was understood about restoring spinal cord function following injury. From this point forward, I wanted to contribute to answering questions commonly asked by SCI patients acutely following injury for which there are currently no answers.

To this end, I began following an academic path toward SCI research by pursuing an undergraduate degree with dual majors in biology and chemistry. This education helped me to understand human anatomy and physiology, and taught me how to critically interpret current literature on treatment options under investigation for restoring function following SCI. To expand my research experience, I applied to the post-baccularate research experience program at the prestigious Mayo Clinic, where I had the opportunity to work for a year in the Regenerative Medicine Laboratory of Anthony Windebank, M.D. This research experience helped solidify my plans of pursuing a career in neuroscience.

Following my tenure in the research experience program, I was accepted into the Mayo Graduate School PhD Program and recruited into Dr. Kendall Lee’s Neural Engineering Laboratory to work on restoration of motor function following SCI via electrical stimulation of the spinal cord. My research has shown that intraspinal microstimulation (ISMS) can restore hind limb function in rodent and swine models of SCI.

Here, I have had the opportunity to collaborate closely with a team of highly skilled neuroscientists, neurosurgeons, biologists, engineers, fellows, and a wide variety of students.

I have been fortunate to be mentored by leading experts in the fields of neuroscience, neurology, neurosurgery, physiology, biomedical engineering, and biomedical imaging. From the personal interactions with my mentors, I have come to understand the commitment it takes to guide junior researchers through their personal career development. From these experiences, I have developed a desire to contribute to the advancement of science through both scientific discovery and by mentoring the next generation of researchers. My career goal is to lead a scientific research team within an academic environment. I am driven by curiosity to find answers to my own personal questions related to SCI recovery, and to help others suffering from neurologic injury.

Presentation abstract:
Intraspinal Microstimulation (ISMS) has been shown to restore function lost due to spinal cord injury (SCI) in several animal models. This presentation will provide an overview of the studies that have led to the emergence of this spinal stimulation strategy for restoration of function following SCI. Additionally, this presentation will describe novel electrical stimulation technologies developed within the Mayo Clinic Neural Engineering Laboratory, including a novel device, MINCS (Mayo Investigational Neuromodulation Control System), which is capable of providing wireless control of spinal stimulation. We tested the ability of MINCS to wirelessly control a custom-designed ISMS system in both a rodent and novel pig model of SCI. ISMS at currents from 10 to 100 µA in rodent and 50 µA to 250 µA in pig activated hip extensor muscles in a proportional fashion.

Our results demonstrate that MINCS successfully evoked controlled movements in paralyzed limbs during remote adjustment of stimulation parameters. These findings show promise for the future of spinal stimulation for restoration of function after chronic paralysis. Further, adaptation of this technology for human use would have the potential to enhance independence for individuals with chronic SCI.

M. Terry Loghmani, PhD, PT, is an Associate Professor at Indiana University (IU) in the School of Health and Rehabilitation Sciences (SHRS), Department of Physical Therapy. She has been on faculty since 1998 and is a certified orthopedic manual therapist with over 20 years of clinical and educational experience in instrument-assisted soft tissue manipulation (IASTM). IASTM is a non-invasive form of mechanotherapy used to address soft tissue dysfunction for a variety of diagnoses. She was recently named director of the SHRS Applied Regenerative Medicine Lab with an overarching goal to contribute to the emerging field of regenerative rehabilitation science. Her primary research interests are in exploring the effects of soft tissue manipulation on tissue healing, repair and regeneration and clinical outcomes in musculoskeletal conditions.

Presentation abstract:
Purpose/Hypothesis: Mechanotherapy interventions, such as instrument-assisted soft tissue mobilization (IASTM) are often used by clinicians to address common musculoskeletal conditions. IASTM is a form of massage that uses rigid devices to deliver a mechanical stimulus to the soft tissue. Initial IASTM animal model and clinical studies have demonstrated positive results. Interestingly, adult stem/progenitor cells (SCs) and massage-based modalities have demonstrated similar therapeutic capacities, e.g. immune-modulation, anti-aging, anti-inflammation and enhanced vascular function. It is also known that SC circulation levels can be altered by disease, age, weight and interventions, e.g. pharmaceuticals, exercise; but the effects of massage/mechanical stimulus on circulating SC levels

remains unknown. It is possible that IASTM stimulates an increase in circulating SC levels which may augment healing. The purpose of this proof-of-concept proposal was to evaluate the acute and cumulative effects of IASTM in healthy young adult males on circulating SC levels and selected clinical outcomes.

Subjects: Six healthy males (18-30y; BMI≥18.5<30 kg/m2) who exercised ≤3d/wk were recruited as an entry-point population since circulating SC levels vary with several factors.

Materials/Methods: In a single setting, within-subjects, pre-, post-test design, subjects received six, 20m sessions of IASTM to the back over 3 weeks by a trained examiner. At the first and last session, peripheral vein blood samples were taken at baseline, after 20m rest, and again after 20m of IASTM. An array of SC subpopulations (circulating endothelial, bone marrow-derived hematopoietic stem/progenitor, tissue-resident mesenchymal stem cells [TR-MSC]) were characterized based on their surface markers by multi-parametric flow cytometry using an established protocol, and self-reported pain/function and physical measures were obtained. Analysis of main outcome measures were determined using paired t-tests ($p<0.05$).

Results: There was a significant, 3-fold, acute increase in the percent of circulating TR-MSCs (CD34+, CD31-, CD45-) from .0012±.0008 to .004±.003 ($p<0.03$). Other outcome measures were not statistically significant.

Conclusions: TR-MSCs are vascular stem cells that reside in the capillaries and adventitia of larger blood vessels throughout the body. Preliminary results suggest that IASTM promotes an immediate increase in circulating TR-MSCs in healthy young adult males. Cumulative effects were not observed, which could indicate a need to better determine treatment timing and dose. Subsequent studies will further characterize the TR-MSCs. It is not surprising that other measures were unaltered in this population. Future research considering the effects of IASTM on SC mobilization, circulation and activity as a function of dose, timing, age, body composition, activity level, gender and disease is warranted.

Clinical Relevance: Findings from this novel pilot study suggest that a form of mechanotherapy, IASTM, has an immediate effect on mobilizing TR-MSCs into circulation; endogenous cells that are critical for vascular repair and tissue healing. This research underscores the significance of tissue-energy interactions as a viable path for non-invasive, mechanical stimuli to potentiate tissue healing and regeneration leading to optimal therapeutic outcomes.

Karina Nakayama, PhD, is a Postdoctoral Fellow at Stanford University. She received her Bachelors of Science in Bioengineering from the University of California, San Diego in 2007. She received her Doctorate of Philosophy in Biomedical Engineering with two designated emphases in Stem Cells and Clinical and Translational Science in 2012. She did her doctoral dissertation on Renal Tissue Engineering with Decellularized Rhesus Monkey Kidneys. Since 2013, she has been a Stanford Postdoctoral Fellow in the Cardiovascular Tissue Engineering laboratory of Dr. Ngan Huang at the Veterans Affairs Palo Alto Health Care System.

Presentation abstract:
Traumatic injury, surgical procedures, or disease may result in impaired endogenous regeneration and revascularization capacity of skeletal muscle. Restoration of vascular and skeletal muscle function using tissue engineering is a promising therapeutic approach. The long-term goal is to engineer skeletal muscle that mimics the physiological orientation of native muscle tissue, in order to examine its

therapeutic potential for improving muscle function in a volumetric muscle loss model. As a starting point, the purpose of this study is to engineer an in vitro muscle that consists of parallel-aligned skeletal myotubes interspersed with parallel-aligned capillaries. We hypothesized that parallel-aligned nanofibrillar scaffolds will guide the organization of skeletal myoblasts and vascular endothelial cells to produce aligned multi-nucleated myotubes interspersed with aligned capillary-like structures. We developed a facile shear-based extrusion technique to create parallel aligned nanofibrillar scaffolds composed of collagen I. Based on scanning electron microscopy, the nanofibrils were uniformly aligned with nanofibril diameters of about 50 nm. Immunofluorescent staining for myosin and endothelial marker, CD31, demonstrated that both cell types rapidly organized their cell bodies along the direction of the nanofibrils and that myoblasts effectively fused to form long myotubes. Development of fluorescently labeled myoblasts (C2C12) and endothelial cells (HMEC-1) using lentiviral transduction enabled live cell imaging and tracking of co-cultured cells on the scaffolds. Current studies to quantify cellular alignment and myotube formation by protein and gene expression assays are underway. Use of primary myoblasts, endothelial cells and fibroblasts is currently being investigated to create a tri-cultured scaffold that would be compatible for transplantation into a volumetric muscle loss mouse model. The in vitro mechanical properties of the co-cultured scaffold were assessed. A marked 4-fold increase in the tensile strength was observed in co-cultured scaffolds compared to cell-free scaffolds, suggesting that cellularized scaffolds more closely resembled muscle-like rigidity. Based on the results of this study, aligned nanofibrillar scaffolds are a potent modulator of cellular organization and are a useful approach to create oriented skeletal muscle.

Linda J. Noble-Haeusslein, PhD, is Professor and Alvera Kan Endowed Chair, Departments of Neurological Surgery and Physical Therapy and Rehabilitation Services at the University of California at San Francisco. The Noble-Haeusslein laboratory studies key determinants of injury and repair in models of traumatic injury to the developing brain and the adult spinal cord. The focus is on the intersection between the innate immune response, matrix metalloproteinases, and specific receptors on leukocytes that modulate demyelination. A second area of research addresses stem cells as modifiers of circuitry that control bladder function and nociception in the injured spinal cord. Using embryonic medial ganglionic eminence cells, the primary source of GABAergic inhibitory interneurons, ongoing studies are evaluating their ability to modify synaptic function and reduce hyperexcitability in circuitry that are responsible for bladder dyssynergia and pain syndromes. Dr. Noble-Haeusslein has recently completed service as a regular member and chair of the NINDS NSDA study section and has contributed to three Institute of Medicine Committees that have addressed traumatic brain injury from the perspectives of its long term consequences and early nutritional support. Her studies on traumatic CNS injuries are funded by the Department of Defense, NIH/NINDS, Craig H. Neilsen Foundation, and the California Institute For Regenerative Medicine.

Presentation Abstract:
Medial ganglionic eminence (MGE)-derived stem cells, when transplanted into the adult murine lumbar cord after a thoracic spinal cord injury (SCI), survive with many of these cells assuming GABAergic interneuron phenotypes. By 6 months post-injury and transplantation, both bladder spasticity/dysfunction and central neuropathic pain (CNP) are attenuated compared to vehicle controls. These findings may result from enhanced GABAergic tone in circuitry controlling bladder function and the emergence of CNP.

Thomas A. Rando, MD, PhD is Professor of Neurology and Neurological Sciences and Director of the Glenn Center for the Biology of Aging at Stanford University School of Medicine. He is also Chief of Neurology at the Palo Alto VA Medical Center where he is Director of the Rehabilitation Research &

Development program whose focus is the emerging field of regenerative medicine. Research in the Rando laboratory concerns the basic biology of stem cells, how stem cells function in adult tissue homeostasis, and how their function is altered in during aging and in response to physical activity. Groundbreaking work from his laboratory showed that much of the age-related decline in stem cell function is due to influences of the aged environmental and can be reversed by exposing the aged cells to a youthful systemic environment. Dr. Rando has received numerous awards, including a Paul Beeson Physician Faculty Scholar in Aging, a Senior Scholar Award from the Ellison Medical Foundation, and a "Breakthroughs in Gerontology" Award from the American Federation for Aging Research. In 2005 he received the prestigious NIH Director's Pioneer Award for his work at the interface between stem cell biology and the biology of aging, and in 2013 he received a Transformative Research Award from the NIH to study the mechanisms of the benefits of physical activity on tissues and stem cells throughout the body, with a particular focus on the "muscle-brain axis" and how muscle activity leads to enhanced neurogenesis and cognitive function.

Presentation Abstract:
Stem cell mediated regeneration of injured or diseased tissue holds great promise as a means to restore tissue structure and function. Our research focuses on the use of muscle stem cells (MuSCs) for the treatment of degenerative disorders of muscle, such as muscular dystrophies, and for treatment of muscle injuries, particularly those characterized as volumetric muscle loss (VML). Toward this end, we have studied the characteristics of MuSCs isolated by fluorescence activated cell sorting (FACS) from mice and from humans to understand the properties that maintain or enhance their potency, following transplantation, to restore normal structure and function to diseased or injured muscle. We have explored regulators of both the transcriptional and epigenetic states of MuSCs to access how treatment *in vitro* can maintain, restore, or induce a highly potent state. In addition, we have focused on important signaling pathways such as the Notch and p38 MAPK pathways and how modulation of those pathways impacts MuSC state and function. Our recent studies of treatment of VML have focused on the use of MuSCs engrafted onto decellularized muscle tissue employed as a scaffold for the transplantation of cells, and how best to enhance the regenerative potential of the MuSCs transplanted within those scaffolds. We have found that including other muscle-resident mononucleated cell populations, such ethothelial cells and fibroadipogenic progenitors (all isolated by FACS), along with MuSCs is superior to MuSCs alone. In an acute VML model, transplantation of MuSCs plus other mononucleated cells leads to better restoration of muscle structure histologically and muscle function physiologically compared to the results with just MuSCs. The inclusion of other mononucleated cells also leads to an enhanced vascularization and more effective innervation of the new muscle formed. Initial studies indicate that muscle structure is also further improved in a chronic VML model when MuSCs are transplanted along with other mononucleated cells compared with MuSCs alone. We are currently analyzing the effects of physical activity on the efficacy of muscle regeneration, and our initial studies show a marked enhancement of tissue restoration when mice engage in physical activity (voluntary wheel running) after cell transplantation for VML injuries. Our long-term goals are to optimize multiple aspects of the process, ranging from the cells to the scaffolds to the physical activity regimen, to generate a scalable process that will lead to effective stem cell-mediated treatment of VML in humans.

Nana Takenaka-Ninagawa, PhD, PT, is a Post-doctoral fellow at Kyoto University, Kyoto, Japan, through a Research Fellowship for Young Scientists of Japan Society for the Promotion of Science (JSPS). Dr. Takenaka-Ninagawa is part of the Department of Clinical Application, Center for iPS Cell Research and Application (CiRA) at Kyoto University, Kyoto JAPAN

She received her PhD in 2013 through the Department of Rehabilitation Sciences at Nagoya University Graduate School of Medicine, Nagoya, Japan, and her BA in 2008 through the Department of Physical Therapy at Nagoya University School of Health Sciences, Nagoya, Japan

Presentation Abstract:
Introduction: Skeletal muscle is one of the tissues that have a high potential for regeneration. And they have their own stem cell; satellite cell. When they damage, satellite cell was activated to regenerate the injured muscle tissues. Because of this character, skeletal muscle seems like a suitable tissue for cell therapy. Although a lot of reports showed effects of cell transplantation toward skeletal muscle disorder and diseases such as Duchenne muscular dystrophy (DMD), the best method of cell transplantation into skeletal muscle have not been considered yet. Therefore our aims of this study was establishment of the most stable and efficient method of cell transplantation into skeletal muscle by using human immortalized myogenic progenitor cell line; Hu5/KD3 (Hashimoto et al. BBRC (2006)).
Methods: Hu5/KD3 was used for this transplantation study. They are expanded and maintained according to the recommended method and transplanted them into cardiotoxin-injured tibialis anterior (TA) muscles of wild type or dystrophin knock out mice (DMD-null mice). To avoid immune rejection of donor cells allowing long-term engraftment, these mice were crossed with the severe immunodeficient mice (NSG mice). We divided the mice into some groups under the following a variety of cell transplanting conditions (inject the cells with ECM or medium, frequency of cell transplantation, and number of injection site etc.) and compared them to find the most effective way for the treatment of DMD and/or injured skeletal muscle. Two weeks and four weeks after transplantation, we evaluate the effect of cell transplantation by histological analysis and functional test respectively. To assess cell graft efficiency we counted the number of muscle fibers expressing human spectrin. Additionally, we evaluate the motor function of cell transplanted muscle by contractile test under anesthesia.
Results and Discussions: We established the novel and effective transplantation method toward injured skeletal muscle. In this symposium, we will introduce the best way of cell transplantation. Now, we are thinking of next plan that is the assessment of transplantation method of human iPS (induced pluripotent stem) cell derived muscle progenitor toward DMD-null mice. This will be a fundamental and important step toward clinical application of cell therapy for injured or diseased skeletal muscle. Furthermore it will be followed by establishment of the effective rehabilitation program combined with cell transplantation. We will try to carry out the rehabilitation trial before and after the cell transplantation into injured skeletal muscle of WT mice or DMD-null mice to find the best way of rehabilitation intervention and show the effect of combination of regenerative therapy and rehabilitation obviously.

Andre Terzic, MD, PhD, has pioneered regenerative medicine at Mayo Clinic. He has authored more than 450 publications, advancing diagnostic and therapeutic strategies for heart failure. His works include team-science efforts in the discovery of genes for dilated cardiomyopathy and atrial fibrillation. He led efforts in the development of next-generation regenerative solutions, including first-in-class products for heart repair. His scientific manuscripts have been cited more than 10,000 times.

Dr. Terzic is Michael S. and Mary Sue Shannon Director, Mayo Clinic Center for Regenerative Medicine, and Marriott Family Professor in Cardiovascular Diseases Research. He is professor of medicine and pharmacology; chair, Discovery-Translation Advisory Board; director, Marriott Heart Disease Research Program; director, National Institutes of Health Cardiovasology Program; and serves on the board of directors, Mayo Collaborative Services.

Focus areas:
•Regenerative medicine and stem cell biology
•Cardioprotection
•Heart failure
•Genetics of cardiac disease and stress tolerance
•Bioenergetic signaling, nucleocytoplasmic communication and ion channel biology
Professional highlights:
•President, American Society for Clinical Pharmacology and Therapeutics
•Chair, Council on Functional Genomics and Translational Biology, American Heart Association
•Chair, Scientific Advisory Board, International Society for Cardiovascular Translational Research
•Martin E. Rehfuss Medal in Medicine
•Henry W. Elliott Distinguished Service Award, American Society for Clinical Pharmacology and Therapeutics
•PhRMA Foundation Excellence in Clinical Pharmacology Award
•Ueda Memorial Award, Japanese Society of Electrocardiology
•Benedict R. Lucchesi Distinguished Award in Cardiac Pharmacology, American Society for Pharmacology and Experimental Therapeutics

To date no presentation abstract has been received.

Carmen Terzic, MD, PhD, received her MD from Mid-Western University in Barquisimeto, Venezuela, in 1987 and her PhD from Mayo Graduate School of Medicine; Rochester, MN, in 1996. Dr. Terzic is the PM&R Department Chair at Mayo Clinic. She holds a joint appointment in PM&R and the Department of Internal Medicine, Division of Cardiovascular Diseases. Dr. Terzic completed her physical medicine and rehabilitation residency at Mayo Clinic before joining the staff. She is active in teaching and research with more than 75 publications in peer-reviewed journals such as Science. Dr. Terzic's research team has engaged in a variety of research efforts to direct stem cells toward cardiogenesis, to assess the role of nuclear transport during stem cell differentiation, and optimize their properties for cardiac commitment. These efforts include developing techniques by which direct injection of stem cells in a murine model of cardiac infarction engrafts and repopulates the diseased heart with cardiac cells derived from the stem cells. The ultimate goal is to establish cardiovascular regenerative medicine as the new therapeutic modality for heart disease.

Presentation abstract:
Cardiovascular disease (CVD) is a leading cause of death, despite advances in pharmacotherapy, revascularization strategies, ventricular assist devices, and organ transplantation complementing cardiac rehabilitation algorithms. Consequently, an interest has been focused on developing other strategies to cure many CVD. In this regard, stem cell technology and the therapeutic value of different types of stem cells have been brought as an emerging tool and have been extensive evaluated in the last 15 years. Pre-clinical studies have shown that progenitor cells can improve the recovery of heart function and is already accepted that circulating bone narrow (BM)-derived stem and several tissue-specific progenitor cells, as well as cardiac residents' stem cells participate in turnover of vascular endothelium and myocardicial repair after cure coronary syndromes. As cardiac rehabilitation is considered 'gold standard' in the care of patients with CVD and exercise training is a key component of cardiac rehabilitation programs, many studies have been also focused on stem cells and exercise-related improvements in the function and regeneration of the cardiovascular system. Results have shown an increment in circulating number of cells in response to acute and chronic exercise, associated with benefits in ventricular function. It has been proposed that the beneficial effects are due to increase in

activation, mobilization, and homing of stem/progenitor cells, together with promoting differentiation of resident tissue-specific cardiac stem cells. Therefore, the use of stem/progenitor cell therapy together with exercise interventions will be instrumental to promote myocardial regeneration for a large spectrum of cardiovascular diseases.

Randy D Trumbower, PT, PhD, is an Assistant Professor and Director of Research within the Department of Rehabilitation Medicine, Division of Physical Therapy, Emory University. He also holds a joint appointment with the Department of Biomedical Engineering, Emory University and Georgia Tech.

Presentation Abstract:
Spinal cord injury (SCI) disrupts connections between the brain and spinal cord, causing devastating loss of mobility and independence. Most injuries are incomplete, leaving intact at least some neural pathways to motor neurons that control movement. Although spontaneous plasticity in these spared pathways underlies some motor recovery, the extent of recovery is slow, variable and frustratingly limited. Thus, there is a critical need for new therapies that promote neuroplasticity and subsequently improve motor function in persons with SCI. One promising strategy to improve motor function is to induce additional spinal plasticity via repetitive exposures to modest bouts of low oxygen (repetitive acute intermittent hypoxia, rAIH). We recently demonstrated that rAIH, alone or in combination with walking training, stimulates motor recovery in persons with chronic, incomplete SCI. The fundamental hypothesis guiding this proposal is that rAIH elicits neuroplasticity, thereby facilitating motor recovery in persons with chronic, incomplete SCI. Detailed mechanistic studies of AIH-induced spinal respiratory and non-respiratory motor plasticity in rats provide a conceptual framework to advance our understanding and optimize functional benefits of rAIH in humans with SCI. The goal of this talk is to present a series of translational studies aimed at uncovering mechanisms of rAIH-induced motor plasticity and recovery after spinal cord injury.

Anthony J. Windebank, MD received his B.A. and M.A. degrees in Biochemistry and M.D. degree from Oxford University in England followed by post-doctoral training at Oxford University, Mayo Clinic College of Medicine and Washington University in St. Louis. Dr. Windebank served as the Dean of Mayo Graduate School from 1992 to 1998 and the Dean of Mayo Medical School from 1998 until 2005. Since 2005 he has been involved in the development and leadership of the Center for Clinical and Translational Sciences at Mayo Clinic and the Center for Regenerative Medicine.

Dr. Windebank is a neurologist who specializes in the diagnosis and treatment of patients with diseases of the peripheral nervous system and spinal cord. Since 1980 he has been involved in the design or conduct of more than 50 clinical trials and clinical studies.

Dr. Windebank is the Past-President of the Peripheral Nerve Society, a fellow of the American Academy of Neurology and the Royal College of Physicians, a member of the Society for Neuroscience and American Neurological Association; and has served on a number of other Boards and Associations. Additionally, Dr. Windebank is a Scientific Reviewer and editorial board member for numerous Journals. Dr. Windebank has served on NIH Study Sections and the Scientific Review Panels for a number of foundations. He has been recognized by a number of national and international awards that include the ETS Walton Fellowship of the Science Foundation of Ireland and a Doctorate (Honoris Causa) from Paracelsus Medical University in Salzburg.

Dr. Windebank's lab research includes repair and regeneration after peripheral nerve or spinal cord injury, treatment of amyotrophic lateral sclerosis and the mechanism of neuronal cell death caused by

chemotherapeutic agents. The laboratory coordinates the research activities of a multidisciplinary team with members from the Departments of Neuroscience, Biochemistry and Molecular Biology, Biomedical Engineering, Physiology, Neurology, Neurosurgery, Physical Medicine, Orthopedics and the Comprehensive Cancer Center.

Dr. Windebank has published more than 400 scholarly articles or abstracts including more than 200 full-length publications in peer-reviewed journals.

Presentation Abstract:
The presentation will describe the rationale for using stem cells in the treatment of neurodegenerative diseases especially amyotrophic lateral sclerosis (ALS) and different types of stem cells that can be used for the treatment of ALS. Ongoing clinical trials of embryonic and mesenchymal stem cells in the treatment of ALS will be discussed.

Tony Wyss-Coray, Ph.D. is a professor of Neurology and Neurological Sciences at Stanford University, the Co-Director of the NIH-sponsored Stanford Alzheimer's Disease Research Center, and the Associate Director of the Center for Tissue Regeneration, Repair and Restoration at the Palo Alto VA. His lab investigates the role of immune responses in brain aging and neurodegeneration with a focus on cognitive decline and Alzheimer's disease. He combines the study of mouse models with human clinical samples using cytomic, proteomic, and bioinformatics tools. He is the recipient of an NIH Director's Transformative Research Award, a Zenith award from the Alzheimer's Association, and a distinguished scholar award from the John Douglas French Alzheimer Foundation. He has been a speaker at the World Economic Forum in Davos and at TED Global in London, and he is the co-founder of two companies and inventor on multiple patents.

Selected honors and awards:
- NIH Director's Transformative Research Award, 2013
- Veterans Administration Senior Research Career Scientist Award, 2012
- Zenith award from the Alzheimer's Association, 2005
- John Douglas French Alzheimer Foundation, 2005
- Current publication record: >1200 citations/year; H-Factor 45

Current research: The Wyss-Coray lab is interested in the role of immune responses and inflammation in brain aging and neurodegenerative diseases. As humans get older many beneficial immune responses decline, while low-level chronic inflammation increases throughout the body. This process, which has been dubbed "inflammaging", is likely to contribute to brain dysfunction associated with aging. Indeed, recent studies from our laboratory have shown that in artificially induced "Siamese" mice, which share a common circulatory system through a process of parabiosis, the blood of old mice is sufficient to induce degenerative changes in the brains of young mice and reduce their memory function. We have isolated blood factors with known functions in the immune system, which are responsible for some of these detrimental effects. By targeting and neutralizing such factors during normal aging or in models of neurodegeneration we are exploring new therapeutic strategies.
On the other hand, in the same model of parabiosis, old mice benefit from exposure to a young circulatory system: old brains show signs of rejuvenation which include increased levels of neurogenesis in a brain region involved in memory formation, reduced neuroinflammation, and activation of genes involved in memory function and cellular remodeling. Moreover, blood plasma harvested from young mice or young humans is capable of improving memory function in old mice or in mice that model

Alzheimer's disease. The lab is now searching for factors in young blood that mediate these beneficial effects.

Presentation Abstract:
Age is the main factor for sporadic forms of neurodegenerative diseases, and aging of peripheral organs may affect brain function. How the systemic environment affects brain health is largely unknown and while some of these interactions may involve cells entering the nervous tissue it is likely that others are mediated by soluble factors. We use a combination of physiological methods to manipulate systemic aging and proteomic methods to try to identify factors that age or potentially rejuvenate the brain. Our findings point to systemic changes in immune responses and cellular signaling factors with aging and may be relevant for the understanding of age-related neurodegeneration.

Moderators that are not also speakers:

Michael L. Boninger, MD
Professor and Endowed Chair
Department of Physical Medicine & Rehabilitation
University of Pittsburgh School of Medicine
Director, UPMC Rehabilitation Institute

Dr. Michael Boninger is a Professor and UPMC Endowed Chair in the Department of Physical Medicine & Rehabilitation at the University of Pittsburgh, School of Medicine. He has joint appointment in the Departments of Bioengineering, and the McGowan Institute of Regenerative Medicine. He is Director of the UPMC Rehabilitation Institute and the Senior Medical Director for Post-Acute Care for the Health Services Division of UPMC. He is also a physician researcher for the United States Department of Veterans Affairs. Dr. Boninger has an extensive publication record of over 200 papers in the areas of spinal cord injury and technology. The technologies Dr. Boninger has investigated vary from brain computer interfaces to wheelchairs. His central focus is on enabling increased function and participation for individuals with disabilities through development and application of assistive, rehabilitative and regenerative technologies. Dr. Boninger also has extensive experience and publications related to training researchers. His students have won over 50 national awards. Dr. Boninger holds 4 United States patents and has received numerous honors, including being inducted into the Institute of Medicine of the National Academy of Science.

Anthony Delitto, PhD, PT, FAPTA is a Professor and Chair, Department of Physical Therapy, and the Associate Dean for Research in the School of Health and Rehabilitation Sciences at the University of Pittsburgh. He is also Vice President for Education and Research Centers for Rehabilitation Services, the largest physical and occupational therapy provider for the UPMC. Dr. Delitto earned his BS in Physical Therapy from SUNY-Buffalo and his MHS/PT and PhD in Psychology from Washington University in St. Louis, Missouri.

Dr. Delitto is primarily interested in conducting evidence-based studies in rehabilitation settings, particularly in populations who have musculoskeletal dysfunction (e.g., low back pain). Most recent completed studies include, "A Randomized Clinical Trial of Treatment for Lumbar Spinal Stenosis" (NIH/NIAMS 1R01AR/NS45622), in which patients diagnosed with lumbar spinal stenosis and consented to surgery were randomly assigned to surgical versus non-surgical intervention and followed initially (6 weeks) and at 2 years after intervention. He is also the site PI for the study, "Exploratory Study of

Different Doses of Endurance Exercise in People with Parkinson Disease: The SPARX Study" (NINDS 1 R01 NS074343), a Phase II study which is to determine the futility or non-futility of conducting a Phase III randomized controlled trial to determine the effects on function of exercise regimens in patients with Parkinson's disease (the SPARX study).

Dr. Delitto was a member of the recently convened Chronic Low Back Pain Task Force at NIH. He is a Catherine Worthingham Fellow of the American Physical Therapy Association (APTA) and has received numerous awards and recognitions from APTA, including the Mary McMillan (2008) and the John HP Maley Lecture Awards, the Lucy Blair Service Award, the Marion Williams Award for Research, and the Helen J. Hislop Award for Outstanding Contributions to Professional Literature. He is a six-time winner of the Orthopaedic Section, APTA's Steven J. Rose Award for Excellence in Clinical Research.

Kimberly S. Topp, PT, PhD, FAAA, is Professor and Chair of the Department of Physical Therapy and Rehabilitation Science and Professor in the Department of Anatomy. She holds the Sexton Sutherland Endowed Chair in Human Anatomy from the UCSF Academy of Medical Educators. Her areas of expertise include anatomy and the application of anatomical knowledge to clinical problems and peripheral neuropathy research. She obtained her BS in Physical Therapy from Northern Arizona University and her PhD in Anatomy and Cell Biology from the University of California, Davis. After completing her post-doctoral training in Neurobiology, Dr. Topp joined the UCSF faculty in 1993. She has received numerous awards including the Henry J. Kaiser Award for Excellence in Teaching in 2006, and Fellow of the American Association of Anatomists in 2010. Dr. Topp has held leadership positions in the American Association of Anatomists and American Association of Clinical Anatomists, and is the current President of the American Association of Anatomists.

Honors & Awards

- ■Henry J. Kaiser Award for Excellence in Teaching, UCSF School of Medicine, 2006
- ■Commitment to Teaching Award, UCSF School of Medicine, 2006
- ■Outstanding Service Award, Academy of Medical Educators, UCSF School of Medicine, 2006
- ■Fellow of the American Association of Anatomists, 2010
- ■Essential Core Teaching Award, Class of 2013, Outstanding Lecture Series, UCSF School of Medicine, 2010
- ■Essential Core Teaching Award, Class of 2014, Outstanding Lecture, UCSF School of Medicine, 2011

Current Research: Dr. Topp's areas of research interest are in structure-function relationships of peripheral nerve and in the application of research findings in the physical therapy clinical population. She has investigated chemotherapy-induced neuropathy in a rat model and human patients. She and colleagues have evaluated sub-clinical and overt sensorimotor neuropathy in study participants with breast cancer treated with taxanes. They documented the sensory neuropathy and measured the correlation between severity of neuropathy and quality of life, level of pain, and balance impairments. These studies are continuing in a funded collaboration with Dr. Christine Miaskowski at UCSF. With collaborator Dr. Benjamin Boyd, Dr. Topp investigated structure-function relationships in normal and injured peripheral nerve. Their published findings using human cadavers supported the use of limb positioning sequences in the physical therapy clinic to induce quantifiable nerve strain during evaluation of nerve dysfunction. They also completed an investigation of biomechanics of the sciatic nerve and related symptomatology in study participants with type 2 diabetes mellitus. Their findings are directly applicable in physical therapy care for this patient population. Dr. Topp's recent perspectives may be seen in the Journal of Hand Therapy, 2012 and Gray's Anatomy, 41st Edition, 2015.

Panelists:

Matthew Muchnick, currently a third year graduate student in Widener University's physical therapy program, Matthew has a strong background in kinesiology with interests to pursue manual therapy and research rehabilitation implications for regenerative medicine. Specific areas of focus include instrument assisted soft tissue message, grade V thrusts for mobility, and proprioceptive neuromuscular reeducation. Matthew's goal in presenting at this year's symposium is to connect with other professionals and students to build interdisciplinary relationships and facilitate physical therapy's involvement in Regenerative Rehabilitation.

Junichi Tajino, PhD, Post-doctoral fellow, Department of Motor Function Analysis, Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Carolina Mie Kawagosi Onodera, MS graduated on Physical Education and Master Degree in Medical Pathophysiology at the University of Campinas. Specialist in Exercise Physiology (CEFIT). Member of the Study and Research group on Physical Exercise and Neuromuscular adaptations. Works in the area of regenerative medicine, physical and functional evaluation in treatment with Platelet-rich Plasma (PRP) in musculoskeletal and vascular diseases. Scientific Assistant at The Bone and Cartilage Institute.

Timothy J. Brindle, PhD, is currently the Scientific Program Manager for the Musculoskeletal Disorders and Medical Comorbidities Program within the Rehabilitation Research & Development Service (RR&D) at the US Department of Veterans Affairs. Dr. Brindle earned his doctoral degree in Biomechanics from the University of Kentucky and a Masters in Physical Therapy from Arcadia University. He completed his post-doctoral fellowship in Rehabilitation Sciences at the National Institutes of Health Clinical Center and collaborated closely with a multidisciplinary research team in his own independent line of study. He was the inaugural director of Walter Reed's Gait Laboratory and has served on many agencies scientific review panels, including: NIDRR, VA, NSF and DoD. He is currently serves as VA's liaison to the Medical Rehabilitation committee for the Interagency Committee on Disability Research (ICDR).

Christopher L. Dearth, PhD is currently the Facility Research Director, Extremity Trauma & Amputation Center of Excellence (EACE) and Director of Research (DoR) at Walter Reed National Military Medical Center (WNMMC). Dr. Dearth is an Assistant Professor in Physical Medicine and Rehabilitation at the Uniformed Services University of the Health Sciences (USUHS).

Ralph M. Nitkin, PhD, is the Program Director for Biological Sciences and Career Development in the National Center for Medical Rehabilitation Research (NCMRR) as well as serving as Deputy Director for the Center. He received his undergraduate and master's degree from the Massachusetts Institute for Technology (MIT) in the area of biological sciences, and his PhD from the University of California, San Diego, in cellular neurobiology. His post-doctoral studies at Stanford University and later work as an Assistant Professor at Rutgers University focused on the cellular and molecular basis of nerve-muscle synapse formation. For the past 23 years he has worked as a Science Administrator at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), first in the area of mental retardation and development disabilities, and currently in medical rehabilitation research. Within the Center, Dr. Nitkin is also active in the area of training and career development.

Hong Chen, MD, PhD, Associate Professor, Department of Rehabilitation, Stem Cell Research Center of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Carmelo Chisari, MD, Dr. Carmelo Chisari received his MD from the University of Padova (Italy). He did his neurology residency at Pisa University (Italy) where he received his Post-graduate specialization in Neurology. He received postdoctoral training in Neuro-rehabilitation and Neurophysiology at the Department of Neuroscience, University of Pisa. From 2003 he is Adjunct Assistant Professor of Neuro-rehabilitation at the University of Pisa. From 2012 he has been Chief of the Laboratory for the study and treatment of motor disorders' at the University Hospital of Pisa. Dr. Chisari's lab is interested in the mechanisms underlying plastic changes in the human central nervous system and in the development of novel therapeutic approaches for recovery of function based on the understanding of these mechanisms. Referee ad hoc for several International Journals in the field of Neuroscience and Neuro-rehabilitation.

Akira Ito, Physical Therapist, PhD, at Kyoto University, Kyoto, Japan. I'm a postdoctoral fellow of Japan Society for the Promotion of Science (JSPS) and study in the Department of Orthopaedic surgery, Graduate School of Medicine, Kyoto University. I got my Ph.D. at the Department of Human Health Sciences, Graduate school of Medicine, Kyoto University on this March.
I've been very interested in the field of Regenerative Rehabilitation since I read the article written by Dr Ambrosio in 2010. My research theme is to clarify effects of thermal stimuli and thermal environment for articular cartilage regeneration.
We, in Kyoto University, are initiating our activity on the Regenerative Rehabilitation this year and I participate in this activity as a program coordinator of our workshop, seminar, and symposium. We will hold 2nd International Symposium on Regenerative Rehabilitation in Kyoto.

Faculty Disclosure

All individuals in a position to control the content of this education activity are required to disclose all relevant financial relationships with any proprietary entity producing, marketing, re-selling or distributing health care goods or services, used on or consumed by, patients.

No relevant financial relationships were disclosed by:

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- M. Terry Loghmani, PT, PhD, MTC
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- Thomas Rando, MD, PhD
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- Carmen M. Terzic, MD, PhD
- Kimberly Topp, PhD, PT
- Randy Trumbower, PT, PhD
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Anthony Windebank, MD
Consultant and Stockholder with BrainStorm Therapuetics
Other: Mayo Clinic has patented intellectual property that will be discussed during the presentation. The property has not been licensed and has not generated any revenue.

Tony Wyss-Coray, PhD
Consultant and Stockholder with Alkahest, Inc.

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POSTER ABSTRACTS

Title: Feasibility study of rehabilitation program after mesenchymal stromal cell transplantation for idiopathic osteonecrosis of the femoral head

Tomoki Aoyama
Department of Physical Therapy, Human Health Sciences, Graduate School of Medicine, Kyoto University

Objective: This study aimed to determine the feasibility and safety of a rehabilitation program that was performed in a clinical trial of mesenchymal stromal cell (MSC) transplantation for idiopathic osteonecrosis.
Methods: The current study was a prospective case series of subjects enrolled in a clinical trial. Ten participants were eligible for enrollment. A 12-week exercise program, which included range of motion (ROM) exercises, muscle strengthening exercises, and aerobic training was performed. All participants underwent assessment before treatment and 6 and 12 months after treatment. ROM, muscle strengthening, timed up and go test, and short form-36 were assessed. Post hoc Scheffe's test was used for statistical analysis. A p value of < 0.05 was considered statistically significant. Adverse events were monitored.
Results: There was significant improvement in external rotation ROM and extensor and abductor muscle strength before and 6 months after treatment ($p<0.05$). Significant improvement was also seen in physical function, role physical, and bodily pain subgroup scores in the SF-36 ($p<0.05$). No serious adverse event was reported.
Conclusions: This study demonstrated the feasibility of a rehabilitation program after MSC transplantation and provides support for further study on the benefits of rehabilitation programs in regenerative medicine.

PLATELET RICH PLASMA COMBINED WITH PHYSICAL THERAPY IN A MIDDLE-AGED MAN WITH KNEE OSTEOARTHRITIS: POSSIBLE ALTERNATIVE TO JOINT REPLACEMENT SURGERY

Morgan Rollo, BS, California Polytechnic State University San Luis Obispo
Kristin L. Bowne, PT MS DPT Center for Rehabilitation and Clinical Research, Scotts Valley, CA

INTRODUCTION: Recent evidence suggests that Platelet Rich Plasma can have a regenerative effect on defects in bone, tendon, and ligaments. [1] [2] These biomolecular pathways include inhibition of the NFkB inflammatory pathway [3], as well as increasing mRNA levels of chondrogenic marker Sox-9 [4]. Patients with these injuries present with pain, stiffness, reduced strength, and loss of functional levels of activity. The purpose of this case report is to describe the use of Platelet Rich Plasma combined with Physical Therapy in a middle-aged man with knee osteoarthritis as a possible alternative to joint replacement surgery, as well as the symbiotic nature of these two interventions.

CASE DESCRIPTION: The patient was a 59 year-old male cyclist and runner presenting with a chief complaint of persistent right knee pain and stiffness with gradual loss of ability to exercise. Evaluation by his orthopedic surgeon yielded recommendation for total joint replacement surgery. Physical therapy examination revealed altered biomechanics, limited knee range of motion and lower extremity muscle wasting. MRI findings demonstrated severe degenerative arthrosis of the knee.

OUTCOMES: The patient received ultrasound guided intra-articular Platelet Rich Plasma injections to the right knee. Physical Therapy was initiated 2 days post injection, which consisted of manual therapy for soft tissue and joint mobilization, eccentric therapeutic exercise for the quadriceps, hamstring and gastrocnemius muscles, and a gradual return to weightbearing exercise and activity. At 4 months post PRP injections and Physical Therapy, the patient reported no pain during daily activities or exercise. Additionally, he had recovered functional gait biomechanics, full knee range of motion, full strength of quadriceps and hamstring muscles, and equalized quad girth in both lower extremities. Additionally he had returned to unlimited walking on all surfaces, agility drills, and road cycling. At 4 months post PRP and Physical Therapy, he had returned to running. Statistically significant improvements were found on WOMAC, VAS, and Global Rating of Change scales.

DISCUSSION/CONCLUSION: In patients with Knee Osteoarthritis, Platelet Rich Plasma combined with Physical Therapy may serve as an effective treatment option.

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Title: Ovarian hormone deficiency alters satellite cell self-renewal following skeletal muscle injury

Brittany C. Collins[1], Robert W. Arpke[2], Vineesha Kollipara[1], Michael Kyba[2], and Dawn A. Lowe[1]
[1]Program in Rehabilitation Science, University of Minnesota, Minneapolis, Minnesota 55455, USA.
[2]Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota 55455, USA.

Satellite cells play an important role in the regenerative capacity of skeletal muscle, in particular their ability to proliferate and differentiate into muscle fibers and then to self-renew (i.e., repopulate the pool of available cells) allows muscle to regenerate after injury. An optimal environment (i.e., niche) is critical for these satellite cell functions and modulation of the niche can significantly alter the regeneration process. We have previously shown that with estradiol deficiency the recovery of strength following skeletal muscle injury is impaired. Moreover, certain aspects of satellite cell function in injured muscle have been shown to be estradiol responsive. The purpose of these studies was to determine a mechanism(s) by which the loss of estradiol impacts satellite function to ultimately impair the functional recovery of skeletal muscle. In study 1, adult C57/BL6J mice were ovariectomized (Ovx) and a subset were treated with estradiol (Ovx+E_2) for 2 months then freeze-injury was induced in the tibialis anterior (TA) muscle. In study 2, adult Pax7-ZsGreen (donors) and NSG-mdx^{4CV} (recipients) mice were either sham-operated (Sham) or Ovx for 2 months. Prior to transplantation of satellite cells, recipient TA muscles were irradiated and cardiotoxin injured. We counted satellite cells by isolating muscles and performing FACS for CD31– CD45– VCAM+ integrin α7+ ZsGreen+ (i.e. Pax7+) cells. The frequency of satellite cells from Ovx mice were significantly lower compared to Ovx+E_2 in uninjured skeletal muscle (P=0.018). To determine if these effects were due to the satellite cell itself or the niche, we transplanted satellite cells from Sham into Ovx mice and vice-versa. Ovarian hormone deficiency of the transplant recipient resulted in a trend for less ZsGreen+ cells compared to the recipient with ovarian hormones (P=0.12). Additionally, Ovx of the recipient caused a significant decline in ZsGreen– cells compared to the sham recipient (P=0.02). Ovx of the transplant recipient also resulted in a lower total number of satellite cells compared to sham (P=0.04). Moreover, ovarian hormone status of the transplanted donor cells had no effect on ZsGreen+ cells (P=0.91), ZsGreen– cells (P=0.24), or total number of satellite cells (P=0.37). However, fiber engraftment did not differ among the transplant recipients or donors (P=0.955, and P=0.532; respectively). Finally, the expression of embryonic myosin heavy chain (eMHC) in muscles of Ovx remained elevated 7-days following injury compared to Ovx+E_2 (P=0.006). These results suggest that estradiol, the most predominant ovarian hormone, modulates satellite cell maintenance by promoting self-renewal which in turn may contribute to the impaired skeletal muscle regeneration with ovarian hormone deficiency.

Characteristics of Traumatically-Injured Patients in the ICU That Distinguish Between Those Who Receive an Order for Physical Therapy and Those Who Do Not: A Retrospective Study

Thomas Ganas,[1] SPT, Emily Lloyd,[1] SPT, Justin Howe,[1] SPT, Pamela Chitika,[2] PT, and Gordon Warren,[1] PhD

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Background: Patients admitted to the intensive care unit (ICU) are at risk for complications secondary to prolonged immobility. These complications result in longer hospital stays, higher healthcare costs, and significant declines in function. Physical therapy (PT) provided in the ICU can be a safe and beneficial means for improving functional status at time of discharge. **Objective:** Analyze the provision and timing of PT orders for trauma patients admitted to the ICU at Grady Memorial Hospital, a Level-1 trauma center in Atlanta, GA. We specifically investigated the patient characteristics that distinguish between patients who receive an order for PT and those who do not. **Methods:** This study analyzed the medical records for all motor vehicle accident (MVA) victims admitted to the ICU at Grady Memorial Hospital between January 2011 and September 2013. These 1677 patients were those involved in an automobile accident, motorcycle/ATV crash, or bicycle/pedestrian vs. automobile accident and were identified from the hospital's trauma registry. Data for this analysis were obtained from the trauma registry and electronic medical records. Patients were divided into two groups, i.e., those receiving orders for PT and those who did not. These patient groups were contrasted on nominal and ratio variable characteristics using Chi-square tests and t-tests (or when appropriate Mann-Whitney tests), respectively. To determine the set of patient characteristics that was most predictive of whether a patient received an order or not, logistic regression analysis was used. The set of patient characteristics that was most predictive of how long it took for a PT order to be written was determined using stepwise regression. **Results:** Seventy-three percent of the 1677 patients received an order for PT before discharge or death, but only 38% received an order while in the ICU. Patients receiving PT orders were 3 years older on average ($p=0.01$) while women received more orders than did men ($p=0.03$). Patients receiving PT orders were more frequently involved in pedestrian versus automobile accidents ($p=0.02$), and scored on average 6 points higher on the Injury Severity Scale (ISS) ($p<0.001$). Patients with PT orders generally had higher Glasgow Coma Scale (GCS) scores ($p<0.001$). Both ICU and total length of stays were longer for patients receiving PT orders ($p<0.001$), who spent, on average, 6 more days in the hospital. The set of factors determined by logistic regression to be most predictive of a patient receiving an order for PT include female gender, a high ISS score, a high GCS score, and involvement in a pedestrian versus automobile accident. Factors associated with fewer days until PT order was written include a low ISS score, high GCS score, female gender, younger age, and a weekday admission. **Conclusion:** Patients sustaining a more severe injury following a MVA, but with good neurological status, were more likely to receive an order for PT services. It is not clear why gender and the type of accident were significant predictors. It is not because they were related to injury severity because the ISS score was also included in the prediction model. Younger, female patients with a lower initial injury severity and good neurological status obtain orders faster. It is also unclear why gender was predictive of time until a PT order is written. **Clinical Relevance:** It is important to identify the factors predictive of whether or not traumatically-injured patients receive an order for PT and how quickly the order is received. This knowledge could be useful in educating the physicians who write the orders for PT. Patients who might not normally receive a PT order might benefit.

Laminin-111 Supplementation Suppresses Inflammation and Fibrosis in Response to Mechanical Overload in Aged Skeletal Muscle

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Introduction: Laminin (LM) is an important extracellular niche protein within the basal lamina that regulates cell structure, function (proliferation, differentiation, adhesion/migration), and survival. The laminin $\alpha1\beta1\gamma1$ (LM-111) isoform is expressed during skeletal muscle development, but then lost in adulthood. Exogenous LM-111 therapy can stimulate satellite cell expansion, new fiber synthesis and myofiber growth in dystrophic and injured skeletal muscle. Thus, the purpose of this study was to determine the extent to which LM-111 could improve age-related deficits in regeneration and growth in response to chronic mechanical loading (CML).

Methods: A modified CML protocol, termed myotenectomy (or MTE) was used to induce bilateral mechanical overload in the soleus and plantaris muscles. Briefly, the myotendinous junction of the gastrocnemius was removed, but the soleus and plantaris muscles were left intact. Animals received a single i.p. injection of saline or LM-111 (1 mg/kg) 1 week prior to MTE. The soleus and plantaris muscles were harvested at day 14 post MTE for biochemical and histological analysis. Exactly 30 min prior to euthanasia, mice were given an i.p. injection of puromycin and peak isometric torque of the posterior crural muscles was assessed.

Results: At 14 days, soleus and plantaris weights were significantly increased in young adult mice in response to loading with saline (soleus MTE main effect $p=0.015$; plantaris MTE main effect $p=0.033$), yet LM-111 provided no additional benefit. Soleus and plantaris weights were not significantly enhanced in response to MTE in aged mice with saline (soleus age main effect $p=0.004$; plantaris age main effect $p=0.003$), yet a trend toward an increase in plantaris weight was noted in LM-111-injected mice. Deficits in peak isometric torque and protein synthesis were established in aged mice and remained unaltered with LM-111 treatment. Interestingly, aged soleus muscles demonstrated an exacerbated immune ($CD11b^+$ cell quantity) and fibrotic (collagen type 1 area) response to loading, and this was abrogated with LM-111 treatment.

Conclusion: LM-111 protein therapy appears to offer protection against inflammation and fibrosis in functionally overloaded soleus muscles in aged mice. Based on published studies, we speculate that LM-111-mediated satellite cell expansion may underlie these beneficial observations. While LM-111 did not acutely alter the hypertrophic response to loading, the results from this study suggest that LM-111 can improve the microenvironment of aged skeletal muscle in a manner that demonstrates potential to maintain mass and function with age.

Effect of BDNF-expressing mesenchymal stem cells on neuromuscular junction denervation after spinal cord injury

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Brain-derived neurotrophic factor (BDNF) signaling is important for the maintenance of structural and functional properties of rat diaphragm muscle (DIAm) neuromuscular junctions. Stem cell-based therapies offer potential for long-term delivery in a targeted manner thus avoiding complications related to off-target effects. Recent work with intraspinal transplantation of adult-derived BDNF-expressing MSCs demonstrated enhanced functional recovery of respiratory activity after cervical C_2 spinal hemisection. We hypothesized that BDNF-expressing mesenchymal stem cells (BDNF-MSCs) can be used to upregulate BDNF signaling in the DIAm, mitigating DIAm denervation and enhancing functional recovery after cervical spinal cord contusion injury. Unilateral contusion was performed on adult male Sprague-Dawley rats at the $C_{4/5}$ level, followed by intra-DIAm injection of vehicle, wild-type MSCs, or BDNF-MSCs (5 sites, 5 x 10^5 cells total). As assessed by whole body plethysmography, a transient ventilatory impairment during hypoxia-hypercapnia was observed at 1 day post-contusion in all groups, with no change during eupnea. Assessments of neuromuscular junction morphometry and evidence of denervation were performed in DIAm whole mounts. Mid-cervical contusion injury resulted in evidence of DIAm denervation in regions consistent with segmental innervation. Contrary to the hypothesis, both wild-type and BDNF-MSCs increased denervation of neuromuscular junctions compared to vehicle injected animals. However, minimal evidence of transplant survival or grafting was found, consistent with avoidance of immunosuppressive therapies in this study. Of note, we had successfully conducted intraspinal MSC transplantation without the need for systemic immunosuppression and thus animals injected intramuscularly were not immunosuppressed. Future experiments will use immunosuppression to evaluate the survival, grafting, fate and efficacy of intramuscular BDNF-MSC injection in mitigating diaphragm muscle denervation following motoneuron injury.

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Poster title:

Dynamic regulation of bone morphogenetic proteins by gentle treadmill walking potentially prevent progression of osteoarthritis in a rat model of destabilized medial meniscus

Abstract:

Objective: This study aimed to evaluate whether long-term gentle treadmill walking could prevent progression of osteoarthritic changes in destabilized medial meniscus (DMM) knee and whether exercise conditions such as timing could affect effectiveness to develop a basis for effective exercise regimen.

Methods: Twelve-week-old male Wistar rats (n = 34) underwent DMM surgery in their right knees and sham surgery in their left knees, and were assigned to either the sedentary (n = 10) or walking (n = 24) groups. The rats in the walking group were subjected to moderate level of treadmill walking from 2-day through 4-week, 4-week through 8-week, or 2-day through 8-week, respectively (n = 8/group). The full analyses, which consisted of micro-computed tomography scanning, histological analysis, and immunohistochemical analysis for detecting osteoarthritic changes of cartilage and subchondral bone, were performed at 8-week after surgery.

Results: Treadmill walking prevented progression of articular cartilage and subchondral bone lesions induced by DMM and upregulated bone morphogenetic protein (BMP) 2 and 6 positive in chondrocytes of superficial zone and subchondral bone lining cells. Furthermore, upregulation of BMPs by treadmill walking was influenced by its conditions; 4-week after the surgery was the best option for the initiation of the treadmill walking to upregulate BMPs which coincide with maximum effectiveness on prevention of osteoarthritic changes.

Conclusion: Treadmill walking could regulate BMPs, that in turn, induced effectiveness on prevention of osteoarthritic changes. A selective timing may be a key for development of optimal exercise regimen to prevent progression of osteoarthritis.

PERIODIC HEAT STIMULUS FOR EXTRACELLULAR MATRIX PRODUCTION ON HUMAN CHONDROCYTES

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Purpose: Autologous Chondrocyte Implantation (ACI) is a cellular therapy to promote regeneration of injured articular cartilages. It is thought that the implanted chondrocytes require optimum microenvironments for re-constructing the tissue. However, the effect of temperature for the implanted cells is not clarified. The temperature in a knee joint is lower than the inner body temperature (approximately 32°C). We hypothesized that periodic heat stimulus would promote the regeneration of the articular cartilage by enhancing extracellular matrix (ECM) synthesis. The purpose of this study was to investigate the effects of the periodic heat stimulus on the ECM production by human chondrocytes *in vitro*.
Methods: The Ethics Committee of the Kyoto University approved the procedure and informed consent was obtained from the donor. Human primary chondrocytes (89-year-old, woman) were cultured using pellet culture method and divided into following three experimental groups: 32°C group which was cultured at 32°C, 37°C group which was cultured at 37°C, and 32°C+heat group which was cultured at 32°C with periodic heat stimulus (41°C, 20 min/day, 6 times/week). The ability of ECM production was evaluated by measuring wet weight and assessing production of collagen and sulfated glycosaminoglycan (GAG) histologically and biochemically. In addition, DNA quantification was performed to estimate cell number.
Results: The wet weight and the GAG production were the greatest in 37°C group but there were no significant difference between 32°C group and 32°C+heat group. The collagen production was the greatest in 37°C group, then in 32°C group, and the least in 32°C+heat group. The amount of DNA was significantly lower in 32°C+heat group than others.
Conclusions: Our results showed that periodic heat stimulus did not promote the cartilage ECM production in the current study conditions, or it might rather repress a collagen synthesis and DNA amount. Temperature of an intra-knee joint is reported approximately 32°C. However, our results indicate that inner body temperature (37°C) would be more suitable for the ECM production than 32°C. Therefore, in order to enhance the ECM production by transplanted chondrocytes after ACI, continuous thermal treatment approximately at 37°C might be suitable to promote its regenerative processes. Further studies are needed to determine the precise influences and the effective setting of the periodic heat stimulus.

Impact of estradiol on inflammatory neutrophils and recovery of strength after traumatic muscle injury in ovariectomized female mice

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Introduction: Ovarian hormones, primarily estrogens, have been reported to influence major post-injury processes, such as inflammation, that affect the recovery of muscle strength. Our previous qPCR data showed increased expression of chemokines/cytokines modulating neutrophil functions as well as increased expression of neutrophil cell surface markers in muscle following injury in estradiol-treated ovariectomized mice. The functional consequences of these estradiol–related inflammatory neutrophil responses are unknown and the role of estradiol in long-term recovery of muscle strength after traumatic injury has not been directly tested. **Purpose:** To determine how estradiol modulates inflammatory neutrophil responses and strength recovery after traumatic muscle injury. **Methods:** Adult, female C57BL/6 mice were ovariectomized and randomly assigned to either no treatment or abdominal implantation of a 17-β estradiol slow-release (OVX+E_2) pellet. Four weeks later, freeze injury was induced to tibialis anterior (TA) muscles and mice were allowed to recover for 1, 2, 3, or 4 days before sacrifice and TA muscle excision. Protein expression level for neutrophil-specific surface marker (Ly6G) in TA muscles was assessed using Western Blot. Myeloperoxidase (MPO) activity, an indicator of neutrophil function, was examined in the muscles. FACS analysis was performed to quantify neutrophil infiltration within the muscles. For assessing the recovery of strength following injury, mice were chronically implanted with a stimulating nerve cuff placed on the common peroneal nerve. Then these nerve cuff implanted-mice were ovariectomized and randomly assigned to abdominal implantation of a 17-β estradiol (OVX+E_2) or placebo (OVX+placebo) pellet. Using this nerve cuff, electrically-stimulated muscle strength was measured immediately before and after injury and at 7, 14, 21 and 28 d post-injury. **Results:** Compared to estradiol-deficient mice, the protein expression of Ly6G in OVX+E_2 muscles increased 60-102% at 1-4 d post-injury (P<0.001). MPO activity was 25-125% greater in the injured muscles of OVX+E_2 mice (P<0.0001). FACS analysis revealed that infiltrated neutrophils were 6-61% greater in injured muscles from OVX+E_2 mice compared to injured muscles from OVX mice, with the peak difference at 4 d post-injury (24±6% [means ± SE] vs 15±3% of hematopoietic cells). The loss of isometric strength immediately after injury was similar for OVX+E_2 and OVX+placebo mice (76±2% vs 79±2%, respectively, from pre-injury, P=0.088). Significant recovery of muscle strength was evident in both groups of mice by 7 d post-injury. At 21 d post-injury, OVX+E_2 muscle had recovered to 100±2% of its pre-injury strength whereas the OVX+placebo mice had only recovered to 78%±3% of its pre-injury strength. The percent of strength recovery was significantly different between the two treatments (P=0.0004). **Conclusion:** Estradiol influences inflammatory neutrophils both quantitatively and functionally. Estradiol does not affect the susceptibility of muscle to freeze injury; however, estradiol deficiency impairs recovery of strength from traumatic muscle injury. Understanding the interaction between estradiol and the injury-induced inflammation, and subsequent recovery of function will be important to develop therapeutic strategies to benefit and improve muscle strength in females with estrogen deficiency. Supported by NIH grant R01-AG031743.

Tissue-Resident Mesenchymal Stem Cells into Circulation

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Purpose/Hypothesis: Mechanotherapy interventions, such as instrument-assisted soft tissue mobilization (IASTM) are often used by clinicians to address common musculoskeletal conditions. IASTM is a form of massage that uses rigid devices to deliver a mechanical stimulus to the soft tissue. Initial IASTM animal model and clinical studies have demonstrated positive results. Interestingly, adult stem/progenitor cells (SCs) and massage-based modalities have demonstrated similar therapeutic capacities, e.g. immune-modulation, anti-aging, anti-inflammation and enhanced vascular function. It is also known that SC circulation levels can be altered by disease, age, weight and interventions, e.g. pharmaceuticals, exercise; but the effects of massage/mechanical stimulus on circulating SC levels remains unknown. It is possible that IASTM stimulates an increase in circulating SC levels which may augment healing. The purpose of this proof-of-concept proposal was to evaluate the acute and cumulative effects of IASTM in healthy young adult males on circulating SC levels and selected clinical outcomes.

Subjects: Six healthy males (18-30y; BMI≥18.5<30 kg/m^2) who exercised ≤3d/wk were recruited as an entry-point population since circulating SC levels vary with several factors.

Materials/Methods: In a single setting, within-subjects, pre-, post-test design, subjects received six, 20m sessions of IASTM to the back over 3 weeks by a trained examiner. At the first and last session, peripheral vein blood samples were taken at baseline, after 20m rest, and again after 20m of IASTM. An array of SC subpopulations (circulating endothelial, bone marrow-derived hematopoietic stem/progenitor, tissue-resident mesenchymal stem cells [TR-MSC]) were characterized based on their surface markers by multi-parametric flow cytometry using an established protocol, and self-reported pain/function and physical measures were obtained. Analysis of main outcome measures were determined using paired *t*-tests (p<0.05).

Results: There was a significant, 3-fold, acute increase in the percent of circulating TR-MSCs (CD34+, CD31-, CD45-) from .0012±.0008 to .004±.003 (p<0.03). Other outcome measures were not statistically significant.

Conclusions: TR-MSCs are vascular stem cells that reside in the capillaries and adventitia of larger blood vessels throughout the body. Preliminary results suggest that IASTM promotes an immediate increase in circulating TR-MSCs in healthy young adult males. Cumulative effects were not observed, which could indicate a need to better determine treatment timing and dose. Subsequent studies will further characterize the TR-MSCs. It is not surprising that other measures were unaltered in this population. Future research considering the effects of IASTM on SC mobilization, circulation and activity as a function of dose, timing, age, body composition, activity level, gender and disease is warranted.

Clinical Relevance: Findings from this novel pilot study suggest that a form of mechanotherapy, IASTM, has an immediate effect on mobilizing TR-MSCs into circulation; endogenous cells that are critical for vascular repair and tissue healing. This research underscores the significance of tissue-energy interactions as a viable path for non-invasive, mechanical stimuli to potentiate tissue healing and regeneration leading to optimal therapeutic outcomes.

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Title: Mechanotherapy: Emerging Evidence for Its Efficacy in Regenerative Rehabilitation

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Purpose: Regenerative rehabilitation (RR) is an emerging field dedicated to the reciprocal integration of regenerative medicine and rehabilitation sciences, ideally at the outset of therapeutic developments, to promote improved outcomes. Rehabilitation science offers examination methods to measure the effectiveness of regenerative therapies, and interventions to influence their responsiveness. Mechanotherapy is often used during rehabilitation and may be defined as therapeutic interventions that use a mechanical stimulus to promote tissue healing. The purpose of this report is to summarize current evidence related to RR regarding the effects of mechanotherapy on tissue healing and regeneration.

Description: A systematic literature search was conducted using PubMed, ProQuest, Science Direct, OVID, CINAHL, and MEDLINE databases. Keywords included RR, regenerative medicine, rehabilitation science, mechanotherapy and physical therapeutics. The search was narrowed to focus on the effects of two regenerative therapy approaches (cellular therapies, tissue engineering) in conjunction with mechanotherapies on neuromuscular and skeletal tissue healing. Only articles published in the last five years where considered.

Summary of Use: Mechanotherapy has expansive implications in RR. In neuromuscular tissues, supervised exercise and other forms of mechanical stimulation may positively impact regeneration. In skeletal tissues (tendon, cartilage, disc, bone), a variety of tissue-specific interventions have been investigated. Mechanotherapy may improve the success of platelet-rich plasma injections used in tendon repair. Several investigations on mesenchymal stem cell injections can be found, in part due to their ability to differentiate into specialized skeletal tissues, but the literature is nearly void of studies determining the optimal application, frequency, duration and timing of physical therapeutics. Regenerative therapies in combination with loading techniques have demonstrated the interaction of mechanical stimulus with biological activity in addressing intervertebral disc dysfunction, once again underscoring the relevance of rehabilitation. In bone and cartilage, regenerative approaches have been combined with physiological loading, vibration and functional mobility to better harness intrinsic tissue-healing properties; but clinical guidelines remain poorly defined.

Importance to Practice: Findings from this review, although not exhaustive, suggest the efficacy of combining mechanotherapy with regenerative therapies for improving outcomes. However, more basic and translational research focused on the use of mechanical stimulus in synergy with regenerative approaches for potentiating innate healing mechanisms is required. Rehabilitation scientists possess a broad range of mechanotherapy interventions within their expertise, in addition to the ability to assess pain, function and physical performance. It is important for researchers and clinicians alike to have an understanding of the effects of mechanotherapy on tissue healing and regeneration, since they are in unique positions to make substantial contributions to the rapidly evolving field of RR leading to viable therapeutic options.

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Opportunities for Advanced Technologies**:** A Physical Therapy Academia Perspective

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Abstract

As rehabilitation specialists, physical therapists must continue to stay current with advances in technologies to provide appropriate rehabilitation protocols, improve patient outcomes, and be the preferred clinician of choice. To accomplish this vision, the physical therapy profession must begin to develop a culture of lifelong learning at the early stages of education and clinical training in order to embrace cutting-edge advancements such as, stem cell therapies, tissue engineering and robotics to name a few. The purposes of this article are to provide a current perspective on faculty and graduate student awareness of regenerative concepts and to advocate for increased integration of these innovative technologies within the doctor of physical therapy curriculum. An online survey was designed to gauge awareness of principles in regenerative rehabilitation, and to determine whether the topic was included and assessed in doctoral curricula. The survey yielded 1006 responses from 82 DPT programs nationwide and indicated a disconnect in familiarity of the term regenerative rehabilitation and awareness of the inclusion of this material in the curriculum. To resolve this disconnect, the framework of the curriculum can be used to integrate new material via guest lecturers, interdisciplinary partnerships, and research opportunities. Successfully mentoring a generation of clinicians and rehabilitation scientists who incorporate new medical knowledge and technology into their own clinical and research practice depends greatly on sharing the responsibility among graduate students, professors, American Physical Therapy Association, and the DPT programs. Creating an interdisciplinary culture and integrating regenerative medicine and rehabilitation concepts into the curriculum cultivates individuals that will be advocates for interprofessional behaviors and will ensure the profession meets the goals stated in APTA Vision 2020.

Engineering Vascularized Skeletal Muscle with Physiologically-Relevant Cellular Organization

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Abstract

Traumatic injury, surgical procedures, or disease may result in impaired endogenous regeneration and revascularization capacity of skeletal muscle. Restoration of vascular and skeletal muscle function using tissue engineering is a promising therapeutic approach. The long-term goal is to engineer skeletal muscle that mimics the physiological orientation of native muscle tissue, in order to examine its therapeutic potential for improving muscle function in a volumetric muscle loss model. As a starting point, the purpose of this study is to engineer an *in vitro* muscle that consists of parallel-aligned skeletal myotubes interspersed with parallel-aligned capillaries. We hypothesized that parallel-aligned nanofibrillar scaffolds will guide the organization of skeletal myoblasts and vascular endothelial cells to produce aligned multi-nucleated myotubes interspersed with aligned capillary-like structures. We developed a facile shear-based extrusion technique to create parallel aligned nanofibrillar scaffolds composed of collagen I. Based on scanning electron microscopy, the nanofibrils were uniformly aligned with nanofibril diameters of about 50 nm. Immunofluorescent staining for myosin and endothelial marker, CD31, demonstrated that both cell types rapidly organized their cell bodies along the direction of the nanofibrils and that myoblasts effectively fused to form long myotubes. Development of fluorescently labeled myoblasts (C2C12) and endothelial cells (HMEC-1) using lentiviral transduction enabled live cell imaging and tracking of co-cultured cells on the scaffolds. Current studies to quantify cellular alignment and myotube formation by protein and gene expression assays are underway. Use of primary myoblasts, endothelial cells and fibroblasts is currently being investigated to create a tri-cultured scaffold that would be compatible for transplantation into a volumetric muscle loss mouse model. The *in vitro* mechanical properties of the co-cultured scaffold were assessed. A marked 4-fold increase in the tensile strength was observed in co-cultured scaffolds compared to cell-free scaffolds, suggesting that cellularized scaffolds more closely resembled muscle-like rigidity. Based on the results of this study, aligned nanofibrillar scaffolds are a potent modulator of cellular organization and are a useful approach to create oriented skeletal muscle.

Knee Osteoarthritis and Platelet-Rich Plasma: Evaluation Methods of Treatment

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Abstract

BACKGROUND: Osteoarthritis (OA) is a chronic joint disease characterized by progressive degeneration of cartilage and bone tissue and synovial inflammation. The platelet-rich plasma (PRP) appears as an autologous therapy, non-immunogenic, able to induce healing and bone repair soft tissue. Therefore, to analyze the effectiveness of a treatment is extremely important to use appropriate evaluation methods. The studies usually use both, the pain and the function as the analysis parameters, through self report questionnaires. On the other hand, the use of physical function tests that can be used in studies of the knee and hip has been recently punctuated in a consensus by researchers. Thus, the purpose of this systematic review was to make a data collection to check which instruments are best used for the evaluation of knee OA treatment with PRP in clinical studies.

METHODS: This study was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). Articles were sought in three databases without specific dates: PubMed, Web of Science and Scopus, clinical studies that cited rich plasma with platelets in a method of treatment, the form of the evaluation and articles in English, entered the study. Studies that have not addressed the treatment of OA of knee using PRP in humans and review articles were excluded.

RESULTS: It was found a total of 313 articles (119 from PubMed, 156 from Web of Science and 36 from Scopus). After an analysis according to the criteria of inclusion and exclusion 28 articles were selected for the study and 14 assessment instruments for knee OA were found. The most widely used questionnaire for the population with knee OA are WOMAC and IKDC. Moreover, many studies have used so associated visual analogue scale (VAS) for evaluating patients' pain levels.

CONCLUSION: The number of clinical studies in knee OA and its treatment with PRP have been growing in the past decade. As noted in this study, the most common form of assessment for the evaluation function is through questionnaires. We confirm that physical function tests are not commonly used in the studies with PRP treatment. We put here our concern mainly on ways to more objective assessment in these treatments to obtain more consistent and comparable data. This could validate the PRP results as an inexpensive treatment, accessible and consolidated.

Effectiveness of Robotic Training after an Acute Muscle Injury in Mice

Authors: Ross Lawrence, Stefano Lai

Abstract: Effectiveness of robotic training after an acute muscle injury in mice

Muscle injuries are prevalent throughout the world and are one of the leading causes of motor dysfunction. Although skeletal muscles have the ability to spontaneously regenerate after receiving damage, the healing process is slower and more functionally incomplete as the severity of the injury increases. Even with the prevalence of muscle injury, the optimal treatment still has not been discovered. It is imperative, then, that efforts towards finding the right approach to enhance skeletal muscle recovery be made. Several studies have shown that mechanical loading and motor exercise has a positive effect on the efficacy of muscle regeneration. Through the use of isolated muscle training from a robotic therapy machine after injury, the superior training method can be observed over time and non-invasively.

We analyzed the effectiveness of robotic training after an injury by subjecting mice to an acute muscle injury followed by various training regiments and eventual myofiber analysis on harvested biceps brachii. The mice were initially trained on the training platform in order to habituate compliant testing responses, like staying in the test-chamber and keeping their wrist in the handle. Mice were then injured via injection of 10 microliters 1µg/µl of cardiotoxin diluted in phosphate-buffered saline solution. Two days after injury, the animals were randomly assigned to three different groups: two groups performed a repetitive and daily task in the robotic platform with a high or low resistance, whereas the third group was not trained. The training was performed 10 trials a day, 4 days a week, for 3 weeks, with loading of 0.3N and 0.1N for high and low groups, respectively. To compare the three groups, all animals were tested on the platform once a week with medium loading intensity of 0.2N. Throughout the testing and training, data on the biceps contractions was collected by the robotic platform. Variables included the force of the contraction and the amount of time between contractions. After 3 weeks, all animals were euthanized and the biceps were harvested and immediately fixed in 2% Glutaraldehyde. The muscles were then cross-sectioned at 10 µm and mounted onto slides. A laminin stain was then performed on the sections collected and, through the use of immunofluorescent imaging, the sites of injury were imaged. With the use of image analysis using NIS-Elements software, the area of each myofiber and quantity of myofibers in every image was calculated. Analysis of the data collected by the robotic platform and the myofiber data revealed no notable difference in muscle function and regeneration at the end of the 3 week program. What was curious, however, was the fact that the mice subjected to the heavy loading program experienced a noticeably faster recovery in force exertion after injury, recovering back to baseline between 9 to 16 days after injury and then plateauing, whereas the mice in the other two groups only returned to approximately base line force levels at the end of 3 weeks. After 3 weeks, there was no difference in myofiber area or number. This is not surprising given that all groups had recovered roughly the same amount by the end of the testing. Future studies should look further into the state of myofiber regeneration throughout the testing phase in order to understand what exactly the cause of this faster force recovery is.

Protease Activated Receptor 2 as a Therapeutic Target to Improve Recovery after Spinal Cord Injury.

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Astrogliosis and inflammation are key integrators of the complex continuum of injury and repair occurring after spinal cord injury (SCI) with molecular drivers representing new therapeutic opportunities. Protease Activated Receptor 2 (PAR2) is a G-protein coupled receptor playing fundamental roles in neural injury, including activities in inflammation and astrogliosis, although its contributions to SCI are essentially unknown. PARs are activated by proteolysis within their extracellular domain revealing a new amino-terminus that binds intramolecularly to elicit intracellular signaling. Thus, PARs enable cells to respond, or to over respond, to rapid changes in the proteolytic microenvironment such as those occurring in traumatic SCI. In this study, we critically evaluated the role and mechanism of action of PAR2 in SCI by determining the impact of PAR2 gene deletion on functional recovery and cellular and molecular signs of pathogenesis in an experimental murine contusion-compression SCI model. Specifically, compression-SCI in PAR2 knockout mice was associated with greater improvements in motor coordination and strength compared to wild type littermates. Molecular profiling of the injury epicenter, and spinal segments above and below, demonstrated mice lacking PAR2 had significantly attenuated elevations in pro-inflammatory cytokine expression (IL-6, TNF and IL-1β) and in key hallmarks of astrogliosis (GFAP, vimentin, neurocan), but enhanced early elevations in the anti-inflammatory cytokine TGF-β. SCI in PAR2-/- mice was also accompanied by improved preservation of PKC-Ɣ-positive corticospinal axons and reductions in GFAP-immunoreactivity, in BIM expression, and in STAT3 signaling. The mechanistic link between PAR2, STAT3 and astrogliosis was investigated in primary astrocytes revealing that the SCI-related serine protease, neurosin (kallikrein 6), promoted IL-6 secretion in a PAR2, MEK1/2- and STAT3-dependent manner. A model is proposed where PAR2-elicited IL-6 secretion drives expression of GFAP, vimentin, and additional IL-6, through canonical STAT3 signaling. Since IL-6 also promoted robust increases in astrocyte PAR2 and neurosin, these data collectively point to an IL-6-driven PAR2 feedback circuit that works hand-in-hand with STAT3 to drive inflammatory-astrogliosis. Given the superior neuromotor recovery observed in PAR2 knockout mice, we suggest that targeting PAR2 to limit inflammation and astrogliosis represents a promising drug target to improve motor outcomes after SCI.

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Interactions between Exercise Training and Dietary Fat Modulate Myelinogensis in the Adult Spinal Cord

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Proper myelination is crucial for transmission of information and myelination is likely modulated by the interaction between lipid components and axonal activity. Here we test the hypothesis that dietary saturated fatty acids alone, or in combination with exercise training, can influence myelin homeostasis in the adult spinal cord. To test this hypothesis, 9 week old adult C57BL6/J male mice were fed a diet enriched in fat (60% total fat, 20% from saturated fat) for a period of 7 weeks, provided access to free wheel running for a corresponding period, or provided access to both interventions in combination. We used quantitative Western blot, real time PCR and immunohistochemical approaches to quantify myelin proteins, oligodendrocyte progenitor cells (OPCs), mature oligodendrocytes, associated growth factor systems, and signaling cascades in the lumbosacral spinal cord of mice under these conditions compared to those with a sedentary lifestyle. Results demonstrate that the abundance of the major myelin membrane proteins, proteolipid (PLP) and myelin basic protein (MBP), as well as NG2, a marker for OPCs, were significantly elevated in the spinal cord after 7 weeks of exercise training in combination with high dietary saturated fats. Expression of MBP and PLP RNA, as well that for Myrf1, a transcription factor driving oligodendrocyte differentiation, were also differentially increased with exercise and/or high dietary saturated fats. In conjunction with these findings however, consumption of a high fat diet alone resulted in a reduction in NG2 and Nkx2.2-OPCs present in the spinal cord white matter of adult mice. A parallel decrease in mature CC-1+-oligodendroglia and those labeled for the pan-OPC and oligodendrocyte marker Olig2 was also seen with consumption of high fat in the context of a sedentary lifestyle. Of potential clinical significance, seven weeks of exercise training completely reversed the deleterious effects of a high fat diet on OPC and oligodendrocyte numbers. Exercise and dietary fatty acid-induced changes in myelinogenesis occurred in parallel with increases in the expression of spinal cord IGF-1 and IGF-1 receptor. Parallel increases in phosphorylated-AKT, a signaling intermediate involved in the myelinogenic effects of IGF-1, was also observed in response to consumption of high dietary saturated fat alone or in combination with exercise. Together these data support a model in which exercise in combination with high dietary saturated fatty acids unleashes a promyelination program that supports myelin homeostasis in the adult spinal cord. These results are crucial for the design of rehabilitative programs to enhance CNS function.

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Targeting the Thrombin Receptor to Improve Spinal Cord Myelination

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Myelination in the CNS is achieved through a delicate balance of extrinsic and intrinsic signaling mechanisms with aberrations in the perinatal period resulting in white matter injury and profound sensorimotor and cognitive disabilities. Leakage of blood-derived serine proteases such as thrombin into the CNS is a common feature of infectious, traumatic, hypoxic and hemorrhagic injuries occurring perinatally. In addition to its roles in thrombostasis, elevations in thrombin have been identified as a powerful neurotoxic agent and possible new target for neuroprotection. Thrombin mediates its cellular effects by activation of a G-protein coupled receptor referred to as Protease Activated Receptor 1 (PAR1). Here we use PAR1 knockout mice to evaluate the role of PAR1 in the process of murine spinal cord myelination at a cellular, molecular and ultrastructural level. PAR1 exhibits peak expression levels in the spinal cord at term, including expression by platelet derived growth factor receptor oligodendrocyte progenitor cells (OPCs) and newly generated CC-1+ oligodendroglia. A critical role for PAR1 in the process of myelination is suggested by findings demonstrating that PAR1 gene deficient mice exhibit an earlier onset of spinal cord myelination, including substantially more Olig2-positive oligodendrocytes, more myelinated axons and higher proteolipid protein (PLP) levels at birth. *In vitro*, the highest levels of PAR1 were observed in OPCs, being reduced with differentiation. In parallel, the expression of PLP and myelin basic protein (MBP), in addition to Olig2, were all significantly higher in cultures of PAR1-/-oligodendroglia. Moreover, application of a small molecule inhibitor of PAR1 (SCH79797) to OPCs *in vitro*, resulted in higher levels of expression of both PLP and MBP upon differentiation. Enhancements in myelination associated with PAR1 deficient mice were also observed in adults, including higher levels of MBP and significantly thicker myelin sheaths across large, medium and small diameter axons. Increases in spinal cord myelination in PAR1-/- mice were coupled to developmental increases in the promyelination signaling intermediates, extracellular-signal-regulated kinase 1/2 and AKT. Nocturnal ambulation and rearing activity were also elevated in PAR1-/- mice. These studies identify the thrombin receptor as a powerful extracellular regulatory switch that could be readily targeted to improve myelin production in the face of white matter injury and disease.

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Age-related declines in Klotho impairs muscle progenitor cell function and skeletal muscle regeneration

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Whereas young skeletal muscle displays an effective regenerative capacity following an acute injury, one of the major concerns with ageing is the dramatic decrease in the regenerative capacity. However, the exposure of aged muscle to a young circulating microenvironment dramatically restores muscle healing capacity. The identification of circulating biomarkers that may underlie these effects remains unclear. One such biomarker is Klotho, a longevity protein that has been associated with tissue regeneration in skin, stomach, small intestine and kidney. When Klotho is disrupted, it promotes an accelerated aging phenotype. Therefore, it is suggested to be a potential biomarker responsible for age-related declines in skeletal muscle regenerative capacity following injury.

In this study, we investigated the expression of Klotho in actively regenerating young and old skeletal muscle. In addition we evaluated the expression of Klotho by muscle progenitor cells (MPCs). Loss-of-function analyses were performed by knocking down Klotho in MPCs using a siRNA. To evaluate how Klotho expression may be related to metabolic activity of stem cells, we performed seahorse analysis of the MPCs to gauge the metabolic activity of young, old and Klotho knockdown in young MPCs.

Confocal microscopy on the injured muscles indicated significantly lower levels of Klotho in old injured animals as compared to the injured young mice, and the same held true for old and young MPCs. Seahorse analysis preformed on the cells suggested that young cells have higher oxygen consumption rate and glycolysis than old MPC counterparts. When Klotho is inhibited in young cells, the bioenergetics profile is brought down to the level of old cells. These experiments suggest that Klotho may be an important biomarker for regenerative potential of aged skeletal muscle.

Study of Cell Transplantation Method towards the Skeletal Muscle Regeneration

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Introduction

Skeletal muscle is one of the tissues that have a high potential for regeneration. And they have their own stem cell; satellite cell. When they damage, satellite cell was activated to regenerate the injured muscle tissues. Because of this character, skeletal muscle seems like a suitable tissue for cell therapy. Although a lot of reports showed effects of cell transplantation toward skeletal muscle disorder and diseases such as Duchenne muscular dystrophy (DMD), the best method of cell transplantation into skeletal muscle have not been considered yet. Therefore our aims of this study was establishment of the most stable and efficient method of cell transplantation into skeletal muscle by using human immortalized myogenic progenitor cell line; Hu5/KD3 (Hashimoto et al. BBRC (2006)).

Methods

Hu5/KD3 was used for this transplantation study. They are expanded and maintained according to the recommended method and transplanted them into cardiotoxin-injured tibialis anterior (TA) muscles of wild type or dystrophin knock out mice (*DMD-null* mice). To avoid immune rejection of donor cells allowing long-term engraftment, these mice were crossed with the severe immunodeficient mice (NSG mice). We divided the mice into some groups under the following a variety of cell transplanting conditions (inject the cells with ECM or medium, frequency of cell transplantation, and number of injection site etc.) and compared them to find the most effective way for the treatment of DMD and/or injured skeletal muscle. Two weeks and four weeks after transplantation, we evaluate the effect of cell transplantation by histological analysis and functional test respectively. To assess cell graft efficiency we counted the number of muscle fibers expressing human spectrin. Additionally, we evaluate the motor function of cell transplanted muscle by contractile test under anesthesia.

Results and Discussions

We established the novel and effective transplantation method toward injured skeletal muscle. In this symposium, we will introduce the best way of cell transplantation. Now, we are thinking of next plan that is the assessment of transplantation method of human iPS (induced pluripotent stem) cell derived muscle progenitor toward DMD-*null* mice. This will be a fundamental and important step toward clinical application of cell therapy for injured or diseased skeletal muscle. Furthermore it will be followed by establishment of the effective rehabilitation program combined with cell transplantation. We will try to carry out the rehabilitation trial before and after the cell transplantation into injured skeletal muscle of WT mice or DMD-*null* mice to find the best way of rehabilitation intervention and show the effect of combination of regenerative therapy and rehabilitation obviously.

Transcriptional differences between bone-derived mesenchymal stem cells and healthy mature articular chondrocytes

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Abstract

Mesenchymal stem cells (MSCs) represent a promising cell source for cartilage regeneration. However, chondrogenesis differentiation using human bone marrow MSCs is far from being understood. In this study, we analyzed 34 microarray profiles to explore differentially expressed genes (DGEs) between human BMSC and chondrocyte, employing bioinformatics strategy attempt to underpin the mechanisms of hBMSC differentiation. Using HG-U133A and HG-U133Plus2 whole genome microarray gene expression profiling, 275 common DEGs were detected between two platforms. Functional enrichment analysis of these common DGEs indicated that TGF-beta and MAPK signaling pathways may play vital role in cell differentiation. Protein-protein interaction (PPI) network was constructed using STRING, by which ACTN1, PTK2, SERPINE1 and TGF-beta 3 were identified to be possibly related to chondrogenesis. In conclusion, our study further identified the potential target genes of hBMSC chondrogenesis and suggests a novel cocktail for hBMSC-derived engineered cartilage.

Cytotoxicity of Local Anesthetics on Mesenchymal Stem Cells - A Systematic Review

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Background: The rapid expansion in knowledge of the trophic, mitogenic, and immunomodulation capacity of mesenchymal stem cells (MSCs) have led to the application of cell therapy as a promising treatment modality for degenerative musculoskeletal conditions, which often are performed under interventional technology. Local anesthetics have been commonly used as part of interventional procedures for alleviating pain during and immediately after injections.

Objectives: The aim of this study is to systematically review in vitro experiments on the cytotoxicity of amide-type local anesthetics (LAs) MSCs.

Methods: We conducted a comprehensive search of five databases, including Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations, Ovid MEDLINE(R), Ovid EMBASE, Web of Science, and Scopus, from each database's inception to Week 22, 2015. Controlled vocabulary supplemented with keywords including 'local anesthetic agent', 'stem cell', 'mesenchymal stem cells', 'toxicity', and a comprehensive list of local anesthetic agents were used for search. Inclusion criteria were: cytotoxic studies of local anesthetic agents on MSCs. Exclusion criteria were: inhalational anesthetic.

Results: Eleven studies were selected from a total of 320 records identified from five databases. All 11 studies were in vitro studies focused on aminoamide-type anesthetics including lidocaine, ropivacaine, mepivacaine, bupivacaine, articaine and prilocaine. None reported on aminoester-type anesthetics. Three comparative studies between the effects of different types of local anesthetic agents showed that ropivacaine has the least detrimental effects on mesenchymal stem cell populations. Lidocaine was reported to have the most significantly effect on stem cell viability. A concentration-dependent as well as a time-dependent effect on viability were reported with bupivacaine, ropivacaine, lidocaine and mepivacaine.

Conclusions: Local anesthetic agents have been reported to have time and concentration-dependent detrimental effects to MSCs. However, in vivo studies would be needed because the concentration and effect time in vivo might be significantly different.

Mesenchymal Stem Cell Therapy for Knee Osteoarthritis: A Systematic review and meta-analysis

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Abstract

Background and purpose: Degenerative knee osteoarthritis (KOA) is characterized by loss of chondrocytes and extracellular matrix in conjunction with accumulation of pro-inflammatory cytokines. Mesenchymal stem cells (MSCs) have attracted interest as a novel therapy because of their trophic effect, mitogenic activity, and immunomodulating capacity. Multiple comparative studies have been conducted to evaluate the efficacy of MSCs in KOA, but often with small sample size, heterogeneous design, and conflicting result. This systematic review and meta-analysis is to summarize the current literature and pool the currently available studies for evaluation of the MSC transplantation for KOA.

Methods: A comprehensive literature search was conducted through Week 16, 2015. Inclusion criteria consisted of Randomized controlled trials (RCTs) and non-randomized controlled trials (N-RCTs). Two reviewers screened abstracts and full texts. Disagreements were resolved by a third reviewer. For continuous outcomes with different measurements, we calculated standardized mean difference (SMD) and for continuous outcomes using the same measurement, we pooled weighted mean difference (WMD) using the D-L random effect models. Heterogeneity between studies was estimated by I^2 statistic.

Results: Of the 522 articles identified, 7 were included in the final analysis. Results indicated that MSC groups are associated with significant improvement in pain reduction (WMD=2.21, 95% CI: 0.66 to 3.77; p=0.005; I^2=98%), activity level (WMD=0.58, 95% CI: 0.36 to 0.81;

p<0.001; I^2=0%), and knee function (SMD=1.15, 95% CI: 0.32 to 1.97; p=0.006; I^2=90%). There was no statistics difference of adverse events between two groups.

Discussion: The current literature shows that intra-articular transplantation of MSCs to the knee joints is effective in pain relief, activity improvement and functional recovery in patients with knee arthritis. Studies showed that the effects were likely associated with well-recognized immunomodulation capacity of MSCs. In the same time, the trophic effect of MSCs increased the duplication and differentiation of the chondrocytes. The increased production of cartilage matrix and hyaluronic acid were also important for knee function.

Conclusions: MSC therapy is a promising novel treatment for KOA. More stringently designed randomized double-blind clinical trials with appropriately determined sample sizes will be needed.

Efficacy of LIPUS treatment following mesenchymal stromal cell intra-articular injection in an osteochondral defect model rats

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Purpose: Mesenchymal stromal cell (MSC) is one of expecting cell sources for cartilage repair. There were some reports that low-intensity pulsed ultrasound (LIPUS), which is used for bone fracture treatment, could stimulate MSC differentiation into osteo-/chondro-cyte. The aim of this study was to investigate whether LIPUS treatment combined with MSC injection could affect cartilage repair for a knee osteochondral defect.

Methods: An osteochondral defect was created on both femur grooves of Wistar rats at 8-week old. Four weeks after the defect creation, bone marrow MSCs diluted with phosphate-buffered saline (PBS) was injected into right knee joint and only PBS injected into left knee joint. The rats were divided into 2 interventions: without or with LIPUS treatment. Two days after injection, the rats with LIPUS were subjected to LIPUS treatment, 20 min/day, 5 days/week, to both knee joints. After 4 and 8 weeks intervention, the rats were euthanized, femora were removed and divided into four groups: Control group, LIPUS group, MSC group and MSCL group (MSC injection with LIPUS treatment). Cartilage and subchondral bone changes were evaluated by histologically with the Wakitani scoring system and micro-CT analysis, respectively. Staining intensity of type II and I collagen was evaluated by immunohistochemical stains.

Results: LIPUS group slightly improved the score, but there were no difference compared with Control group at 4 weeks after intra-articular injection, and the improvement didn't continue at 8 weeks after intra-articular injection. MSC and MSCL group were significantly improved compared with Control group. The expression of collagen type II was observed in wide range of repair tissue in LIPUS, MSC and MSCL group, but the expression of type I collagen was observed through surface and middle zone in these groups. By the micro-CT analysis, irregularity of the surface on subchondral bone were slightly improved at 8 weeks after in MSCL group compared with other groups.

Conclusions: MSC injection combined with LIPUS treatment couldn't significantly improve cartilage repair score compared with MSC single injection, but it might promote type II collagen expression and type I collagen decline in repaired cartilage, and promote subchondral bone formation.

Title: Why do dental pulp stem cells lose differentiation capability at *in vitro* culture?

Shaomian Yao and Michael Flanagan

Introduction: Adult stem cells (ASCs) lose their differentiation capabilities during *in vitro* culture. This is one of the major hurdles in applications of adult stem cells (ASCs) as *in vitro* expansion is usually needed to obtain a large number of cells for tissue regeneration or tissue engineering applications. Currently, it is largely unknown why ASCs lose their differentiation capability during *in vitro* culture. Elucidation of the factors causing the loss of differentiation could lead to development of methods to maintain differentiation capability in expansion of the ASCs. This study was to explore the potential factors causing loss of differentiation in the dental pulp stem cells (DPSCs) at *in vitro* culture.

Experimental Methods: DPSCs were isolated from the first mandibular molars of postnatal rat pups. Cells were cultured in T-25 flasks to 90% confluency for passage. Cells at passages 3, 5, 7, 9 and 11 were collected for RNA isolation. Concurrently, cells of different passages were subjected to osteogenic induction to determine their differentiation capability. Expression of stem cell markers in early, late passages of DPSCs and non-stem cell dental pulp cells was compared. Whole genome microarray study was conducted to compare the changes of gene expression profile in the early passage vs. late passage DPSCs. These changes in gene expression were confirmed by real-time RT-PCR. Based on this, candidate genes were selected and siRNA was used to knockdown the expression of the candidate genes in early-passage cells to determine their effect on maintaining osteogenic differentiation capability. Statistical analysis of the data were done using SAS program with ANOVA and LSD at $P< 0.05$.

Results: Strong osteogenic differentiation was observed in passages 3 and 5 (P3 and P5). This capability was greatly reduced at passage 9 (P9) and completely lost at passage 11 (P11). However, expression of typical stem cell marker genes was much higher in DPSCs as compared to non-stem cells, and was similar in early and late passages of DPSCs, indicating that the loss of differentiation was not due to overgrowth of non-stem cells. P3 DPSCs expressed significantly higher levels of Thrombomodulin (Thbd); GIPC PDZ domain-containing family, member 2 (Gipc2); Heat Shock Protein B8 (HspB8); Zinc Finger Protein 423 (Zfp423); and Kruppel-Like Factor 5 (Klf5) when compared to P11 DPSCs. Knockdown of Zfp423 and HspB8 expression in early passage DPSCs resulted in loss of osteogenic capability similar to that was seen in the late-passage DPSCs. In contrast, no change in osteogenic capability was observed after knockdown of Thbd, Gipc2, and Klf5 in early passage DPSCs.

Conclusion: Zfp423 and HspB8 appear to play important roles in maintaining osteogenic differentiation capability in DPSCs. The reduction of the expression of these two genes is likely responsible for loss of osteogenic differentiation seen in cultures of DPSCs.

Travel Awards:

These grant are intended to provide opportunities for graduate students, medical fellows and residents, post-doctoral fellows, rehabilitation clinicians, and junior investigators to participate in the Fourth Annual Symposium on Regenerative Rehabilitation, to be held in Rochester, MN on September 24-26, 2015.

Congratulations to all of our recipients!

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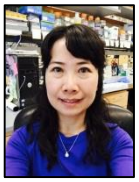
Genyun (Coco) Le University of Minnesota	
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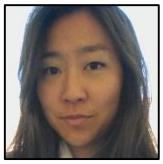
Karina Nakayama Stanford University	
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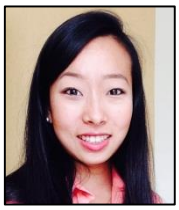
Carolina Mie Kawagosi Onodera Universidale Estadual de Campinas Campinas, Brazil	
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