

**6<sup>th</sup> Annual International Symposium on Regenerative Rehabilitation**  
**Nov. 1-3, 2017**  
**Post-Meeting Summary**

Cutting edge, inspirational, time well spent – all words that describe the 6th Annual International Symposium on Regenerative Rehabilitation held in Pittsburgh, on November 1-3, 2017. The Symposium was co-hosted for the first time through an international collaboration formed by the University of Pittsburgh (UPitt) and Kyoto University, Japan. Regenerative Rehabilitation is an innovative and emerging field representing *a fusion of disciplines across the domains of regenerative medicine and rehabilitative science*, ultimately resulting in improved functional outcomes for patients. Once again the Symposium created a forum for researchers and clinicians from multiple disciplines to explore the interaction of physical therapeutics with regenerative medicine across a variety of disease conditions.

At a pre-conference roundtable discussion, leaders from the International Consortium on Regenerative Rehabilitation (ICRR) gathered with federal agency delegates, organizational leaders, scientists, and clinicians. This created a platform for multiple stakeholders to share their insights and strategies on how to move the field of regenerative rehabilitation forward with rapid translation. The group identified needs for rigorous peer review, development of standards of care, and validation of complementary and integrative approaches to pain. Studies should align with agencies' priorities, while considering the synergistic mechanisms and effects of rehab and cell therapies on tissue function and, importantly, functional outcomes - not just on diagnostic tests. Momentum is building in Regenerative Rehabilitation as evidenced through an increase in related publications and a broadened exposure through other venues. For example, leaders in the field will be presenting a Regenerative Rehabilitation Workshop at the Orthopaedic Research Society. The group wholeheartedly agreed that continued partnerships in rehabilitation and regenerative medicine are needed to help the field evolve.

At the opening event, Gwendolyn Sowa, MD, PhD, Department of Physical Medicine and Rehabilitation, University of Pittsburgh School of Medicine, extended a warm welcome to attendees and moderated a special session on *Regenerative Rehabilitation for Traumatic Brain Injury (TBI)*.

Esteemed researcher Rocky S. Tuan, PhD, University of Pittsburgh School of Medicine, gave a high energy presentation, *Overview and Development of TBI Research Program at Pittsburgh*. He highlighted the goal of the new traumatic brain injury (TBI) research center at UPitt, TEAM-TBI. Its mission is to develop and improve precision medicine strategies for the heterogeneous population of patients suffering from TBI.

Steven W. Levison, PhD, Department of Pharmacology, Physiology and Neuroscience, Rutgers University, presented *Cell Replacement After Traumatic Brain Injuries: Contributions of Resident vs. Transplanted Neural Stem Cells*. Neurons for neurogenesis are located in different zones of the brain that are generated at different times in development. He indicated native neural stem cells are activated following injury and if these cells do not undergo activation and migration in a proper sequence, regenerated tissue will look more like a scar and yield poorer outcomes. Figuring out how to provide the right cues for sequential activation and migration of neural stem cells is critical.

Patrick M. Kochanek, MD, Children's Hospital of Pittsburgh of UPMC, gave a passionate presentation on *New Therapies for TBI, Operation Brain Trauma Therapy (OBTT) and Beyond*. His talk emphasized the importance of balancing innovation with scientific rigor. He pointed out problems associated with

reproducibility of findings on pharmacological interventions for TBI – the main issue being poorly controlled studies. When data are passed through stringent filters, very few pharmacological agents actually show a clear benefit for TBI. Properly controlled studies have shown promise, but for a drug to be proven effective, it must be shown to promote recovery of physical and cognitive function.

Elizabeth R. Skidmore, PhD, OTR/L, Department of Occupational Therapy School of Health and Rehabilitation Sciences, University of Pittsburgh, rounded out the session by presenting on *Optimizing TBI Rehabilitation to Promote Regeneration and Recovery*. She emphasized the importance of seeing through the eyes of the client as rehab scientists and determining how we can optimize outcomes via personalized rehab based on TBI phenotypes. Rehab interventions must be task specific, meaningful, challenging, and goal oriented.

The evening closed with a robust discussion by all four presenters who emphasized the need for research that considers the heterogeneity of disease conditions and individuals' responses, along with the development of targeted outcome measures. The panel discussion was followed by a reception complete with hors d'oeuvres, a wine bar, and wonderful live music played by a guitar-violin duo.

The second day began with a *Special Interest Group: Clinician Breakfast / Networking* session led by Carmen Terzic, MD, PhD, Mayo Clinic, and William Thompson, DPT, PhD, Indiana University. Clinicians and students shared excitement and ideas about Regenerative Rehabilitation over breakfast while debating and brainstorming clinical strategies.

The Symposium officially opened with an enthusiastic welcome and introduction by symposium co-chairs: Fabrisia Ambrosio, PhD, MPT, Department of Physical Medicine and Rehabilitation, University of Pittsburgh, and Hiroshi Kuroki, PT, PhD, Rehabilitation Science for Bone and Joint Disorders Human Health Sciences, Kyoto University, Japan. They told the "story of us" - about how the field has evolved, and how Kyoto University became a co-host with the University of Pittsburgh for the 2017 Symposium through a productive collaboration of investigators from both institutions. Drs. Ambrosio and Kuroki announced the academic cooperation that has been formed between the Schools of Medicine from both institutions, with the goal of promoting research collaborations and the exchange of ideas in the domain of Regenerative Rehabilitation. Dr. Kuroki concluded by inviting participants to attend the TERMIS World Congress, which will be held in Kyoto in 2018.

Keynote speaker, David J. Mooney, PhD, John A. Paulson School of Engineering and Applied Sciences, Harvard University, provided an insightful talk on *Exploiting Mechanics to Promote Regeneration*. He emphasized that the viscoelastic properties of native tissue and engineered substrates are of particular significance in determining stem cell fate. He pointed to new directions in regenerative mechanobiology including robotics, newer soft tissue adhesives for delivery of therapeutic agents, and gel-coated stem cells for better immuno-protection during delivery.

The morning session, *Applied Mechanobiology*, was moderated by Nick Willett, PhD, Emory University School of Medicine.

Adam Feinberg, PhD, Departments of Materials Science & Engineering and Biomedical Engineering, Carnegie Mellon University, talked about how muscle tissue organizes itself in his presentation, *Advanced Biofabrication Strategies for Engineering 3D Muscle Tissue*. He focused on cardiomyocyte differentiation and the importance of extracellular matrix organization for cellular function.

Thomas A. Rando, MD, PhD, School of Medicine, Stanford University, presented *Regenerative Rehabilitation Therapy for Volumetric Muscle Loss*. The failure of tissues to regenerate from volumetric muscle loss (VML) may be attributed in part to the lack of an adequate tissue scaffold. His research uses VML animal models to test regenerative rehabilitation interventions such as muscle electrical stimulation. His findings suggest implanting or injecting some non-muscle cells into the region of VML may improve regeneration since muscle is composed of various cell types.

Hidetoshi Sakurai, MD, PhD, Center for iPS Cell Research and Application, Kyoto University, Japan, gave an interesting perspective on *Regenerative Therapy for Muscle Dystrophy by Transplantation of Muscle Stem Cells Derived from Human iPS Cells*. He underscored findings that induced pluripotent stem cells (iPS) expressing certain myogenic regulatory factors are better at promoting myogenesis; and, conversely, if certain factors are missing, they may tend to create tumor-like cells.

Ngan Huang, PhD, School of Medicine Stanford University, presented a talk on *Physiologically Oriented Engineered Skeletal Muscle for Treatment of Volumetric Muscle Loss*. Using live animal imaging and histological study, her research has revealed that aligned scaffolds promote better regeneration than random scaffolds following VML. Better vascularization is also found with aligned scaffolds plus exercise.

Selected oral presentations were given by Sarah M. Greising, PhD, US Army Institute of Surgical Research, *Pathologic Fibrosis Progressively Increases following Volumetric Muscle Loss Injury*; and Svyatoslav Dvoretzkiy, MS, University of Illinois, *Pericyte Response to Muscle Contraction*. By the end of this session, attendees had received a broad overview of mechanobiology and how environmental influences impact regenerating cells.

Following lunch, the focus on *Applied Mechanobiology* continued into the first afternoon session moderated by Christopher Evans, PhD, Mayo Clinic.

Martin Stoddart, PhD, AO Research Institute Davos, Davos Platz, Switzerland, presented on *Multiaxial Load as a Driver of Human MSC Chondrogenesis*. His research has found that the development of cartilage in culture requires appropriate growth factors and mechanical loading. In particular, combined compressive and shear forces produce better cartilage in vitro.

Keiji Naruse, MD, PhD, Okayama University, Japan, gave a talk on *Mechanomedicine: Mechanobiology and Its Implications for the Field of Regenerative Rehabilitation*. The importance of the stretch-activated calcium channel's role in mechanobiology was emphasized. He coined the term "mechanomedicine," which resonates well with the concepts of mechanotherapy.

William Thompson, DPT, PhD, School of Health & Rehabilitation Sciences, Indiana University, presented *Mechanical Control of MSC Fate: The Role of the Actin Cytoskeleton*. Mesenchymal stem cells will differentiate into osteoblasts, adipocytes, or myoblasts depending on the influence of different factors. He is working to identify key molecules in the signaling cascade leading to osteocyte differentiation.

By the end of the second session on *Applied Mechanobiology*, the audience had a good appreciation for the role of mechanical forces as well as molecular signaling in stem cell maturation and regenerative medicine outcomes.

The next session, *Neurologic Applications of Regenerative Rehabilitation*, was moderated by Linda Noble-Haeusslein, PhD, The University of Texas at Austin. This session gave the audience an overview of the role of environmental cues and forces, as well as rehabilitative techniques, for optimizing cell-based therapies for neurological deficits.

Thomas Carmichael, MD, PhD, Department of Neurology, University of California Los Angeles, discussed *Re-Building Brain Tissue After Stroke*. The most plastic region surrounds the area of stroke and greater plasticity correlates with better outcomes. Additionally, angiogenesis promotes neural growth. Interestingly, he has found that implanting hydrogel matrices into the “stroke cavity” increases angiogenesis and, therefore, neural plastic changes. Hydrogel matrices could be engineered for release of selected growth factors.

Michel Modo, PhD, Department of Radiology, University of Pittsburgh, presented *Exploring Synergistic Effects of Physical and Cell Therapy in Stroke*. He uses a mouse model of stroke in his research to explore the effectiveness of cell therapies in combination with rehabilitation.

Lawrence R. Wechsler, MD, Department of Neurology, University of Pittsburgh School of Medicine, discussed *Clinical Trials of Stem Cell Transplantation for Treatment of Stroke*. Homing factors that attract stem cells cease to be released in chronic stroke (approximately 2-years post-onset). At that point, only local delivery (vs. systemic delivery) of stem cells into the stroke region has been found to help. A stem cell preparation can improve outcomes, most likely through its anti-inflammatory effects.

Carmelo Chisari, MD, Unit of Neurorehabilitation, University Hospital of Pisa, Pisa, Italy, gave a talk on *Clinical and Neurophysiological Evidences of Brain Plasticity*. He has found that aerobic exercise improves cognitive function post-stroke. Also, transcranial magnetic stimulation (TMS) improves outcomes in patients who had similar sized lesions as a control group.

George Kraft, MD, Department of Rehabilitation Medicine and Neurology, University of Washington, spoke on *The Use of Autologous Stem Cells in Rehabilitation of Multiple Sclerosis*. Patients with multiple sclerosis were injected with non-conditioned naïve CD34+ stem cells after ablating the immunoactive blood cells, and this was followed up with tailored rehabilitation protocols. Their findings indicated that patient selection was key, as responders to this form of treatment were early in their disease, had very active inflammatory MS, and RRMS-type of MS rather than SPMS or PPMS.

Shang Song, PhD, Stanford University School of Medicine, gave an oral presentation, *Conductive Conduits to Augment Cell Therapy for Peripheral Nerve Injury*. Her research examines the use of a conductive polymer scaffold that allows for electrical stimulation of human neural stem cells in order to optimize recovery for the treatment of peripheral nerve injury.

A poster session and networking reception then followed. Congratulations are extended to the poster awardees: 1st place- Hikaru Mamiya (UPitt), 2nd place- W. Michael Southern (University of Georgia), 3rd place- Jr-Jiun Liou (UPitt).

A Special Session Panel Discussion: “Glories, Gripes & Grapes,” moderated by Michael Boninger, MD, University of Pittsburgh, topped off the evening. Panelists included: Esther E. Dupont-Versteegden, PhD, University of Kentucky; G. Kelly Fitzgerald, PT, PhD, UPitt; Ralph Nitkin, PhD, Health Scientist Administrator, NIH (NICHD); and, Kimberly Topp, PT, PhD, University of California San Francisco. Take home messages included: the importance of focusing on patients’ individual rehabilitative needs; for

studies to include sham groups to tease out the influence of other effects; and the importance of educating clinicians, scientists, and students on the value of rehabilitation being coupled with regenerative interventions. Other priority areas underscored were developing better abilities to generate tissues versus merely delivering cells; establishing standardized terminology and protocols for rehab interventions; implementing goal-oriented and task-specific rehab interventions; and validating targeted functional measures.

The final session of the symposium, *Translate Your Science: Regenerative Rehabilitation Technologies, Methods & Approaches*, was moderated by Terry Loughmani, PT, PhD, Indiana University.

Ryosuke Ikeguchi, MD, PhD, Department of Orthopaedic Surgery and Rehabilitation Medicine, Kyoto University Graduate School of Medicine, Japan, gave an excellent overview on *Rehabilitation and Regeneration of Peripheral Nerve Injury*. He discussed state-of-the-art repair and regeneration approaches for various nerve injuries. Findings suggest that nerve repair or transplant in combination with appropriate exercise leads to optimized outcomes.

Koichi Nakayama, MD, PhD, Department of Regenerative Medicine and Biomedical Engineering, Saga University, Japan, gave an *Introduction of Scaffold-Free Bio 3D Printer for Organ Regeneration*. He used impactful images and entertaining videos to illustrate his work on “scaffold-free” tissue engineering using “cell balls” that are “skewered” into meta-structures with the help of mechanical stimulation. This technology offers an alternative to scaffolds, which can introduce pathways for infection and may impose limitations to regeneration. So far, excellent results have been found when the scaffold-free tissues are wrapped around ruptured blood vessels or implanted into cartilage defects.

Robert Gaunt, PhD, Physical Medicine and Rehabilitation, University of Pittsburgh, discussed *Human Brain-Computer Interfaces for Sensorimotor Science and Rehabilitation*. His fascinating work focuses on Brain Computer Interface (BCI). For BCI to work well, it must properly isolate, acquire, and translate neural information, and utilize those neural signals to produce movement or perceive sensation. Grid electrodes that wrap around target regions of the brain are capable of providing and receiving information to not only control but to receive sensory input from the robotic arms in amputees.

Shawn Russell, PhD, Department of Orthopedic Surgery, University of Virginia, presented *Quantifying Comprehensive Evaluation of VML Injury and Repair in Animal Models: From Biological Relevance to Biomechanics* on behalf of George J. Christ, PhD, Departments of Biomedical Engineering and Orthopedic Surgery, University of Virginia; and *The Impact of TA VML Injuries on Rat Gait*. Better functional outcome measures are needed for preclinical studies. They have developed creative and highly technical research methods for collecting kinematic and kinetic data from rodents during voluntary walking/running using 3D motion analyses and inverse dynamics modeling (with a force platform). Findings demonstrate rodents with VML may have gait defects similar to humans.

James J. Irrgang, PT, PhD, School of Health and Rehabilitation Sciences, University of Pittsburgh, presented *Evaluating Clinical Outcomes of Biological Treatments*. He provided a well-organized and clear schematic overview of suitable outcome measures for rehabilitation research that correspond to the International Classification of Functioning (ICF) model.

Jack Dienes, Department of Biomedical Engineering, University of Virginia, gave an oral presentation on the *Comprehensive Characterization of Rodent Gait Kinetics and Kinematics as a Standard of Comparison for Regenerative Therapies*. He reported that they have developed a database of normal gait parameters

in a rat model that can be used as a baseline for evaluating VML injuries and the effectiveness of regenerative therapies.

By the end of this session, attendees had a better appreciation of how technological advances are being used to both enhance Regenerative Rehabilitation outcomes as well as to assess the effectiveness of Regenerative Rehabilitation outcomes.

Post-symposium Regenerative Rehabilitation Research Workshops were offered for the first time. The two concurrent sessions were: *Clinical Study Design for Regenerative Rehabilitation*, facilitated by Marcos Bamman, PhD, University of Alabama; and *Rehabilitation Strategies in Preclinical Models: An Overview of the Fundamentals* led by Linda Noble-Haeusslein, PhD, University of Texas, and Gordon L. Warren, III, PhD, Georgia State University. These tracks highlighted the importance of scientific rigor and reproducibility in all studies; gender as a biological variable; relevant functional outcome measures; appropriate translation of animal model findings to humans; and the heterogeneity of individuals and disease conditions pointing to the need for precision rehabilitation.

In closing the Symposium, Dr. Ambrosio reinforced the impetus for Regenerative Rehabilitation efforts, which span the gamut from molecular mechanisms to clinic functional performance. With great optimism, she stated, “In regenerative rehabilitation, we must become at ease with the overwhelm felt from the atom-smashing of the different worlds of emerging technology, surgery, medicine, and basic and clinical science.” Regenerative interventions that are more tissue-based than cell-based are needed and must be task-specific, meaningful to patients, and relevant to functioning in the real world. She urged educators to incorporate Regenerative Rehabilitation content into curricula, and for clinicians and scientists to interact closely to move the field forward. All are invited to the 7<sup>th</sup> Annual Regenerative Rehabilitation Symposium in Fall 2018, to be hosted at the University of Washington in the beautiful city of Seattle.

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