Conference Report

Regenerative Medicine

Conference Report: 6th Annual International Symposium on Regenerative Rehabilitation

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The 6th International Symposium on Regenerative Rehabilitation, hosted by the Alliance for Regenerative Rehabilitation Research and Training (AR^{3}T), included a preconference meeting of institutional representatives of the International Consortium of Regenerative Rehabilitation, keynote talks from distinguished scientists, platform and poster presentations from experts and trainees, panel discussions and postconference workshops. The following priorities were identified: increasing rigor in basic, preclinical and clinical studies, especially the use of better controls; developing better outcome measures for preclinical and clinical trials; focusing on developing more tissue-based interventions versus cell-based interventions; including regenerative rehabilitation in curricula of professional programs like occupational and physical therapy; and developing better instruments to quantify rehabilitative interventions.

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The 6th Annual International Symposium on Regenerative Rehabilitation took place in in Pittsburgh (PA, USA) on 1–3 November 2017. The overarching purpose of the symposium is to serve as a setting that brings together an international community of renowned scientists and clinicians focused on regenerative rehabilitation for presentations, dialog and networking. Regenerative rehabilitation is an emerging field that synthesizes two disciplines, regenerative medicine and rehabilitation, into a single field which aims to translate discoveries in tissue engineering and cellular therapies into treatments that optimize functional outcomes in patients across a variety of neuromusculoskeletal disorders. The symposium is sponsored annually by a multitude of entities, most notably the Alliance for Regenerative Rehabilitation Research and Training (AR^{3}T), and the University of Pittsburgh (UPitt) McGowan Institute for Regenerative Medicine, PA, USA. The 2017 symposium was co-hosted for the first time through an international collaboration formed by UPitt and Kyoto University (Kyoto, Japan). What follows are conference highlights from keynote speakers and themes.

Prior to the conference proceedings, leaders from the International Consortium on Regenerative Rehabilitation gathered with federal agency delegates, organizational leaders, scientists and clinicians at a roundtable discussion to share their insights and strategies on how to move the field of regenerative rehabilitation forward. The group identified important needs for rigorous peer review, development of standards of care and validation of complementary and integrative approaches to pain. The group wholeheartedly agreed that continued partnerships in rehabilitation and regenerative medicine are needed for the field to evolve.

At the opening event, Patrick M Kochanek (University of Pittsburgh Medical Center), gave a passionate presentation entitled 'New therapies for traumatic brain injury, operation brain trauma therapy 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 traumatic brain injury, such as poorly controlled studies [1]. The evening closed with a robust panel discussion held by Dr Kochanek and the other three presenters from the opening event: Rocky S Tuan (UPitt), Steven W Levison (Rutgers University, NJ, USA) and Elizabeth

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Skidmore (UPitt). The discussion underscored the need for research that considers the heterogeneity of disease conditions and individuals' responses, along with the development of targeted outcome measures.

The symposium officially opened the next day with an enthusiastic welcome and introduction by symposium co-chairs Fabrisia Ambrosio (UPitt) and Hiroshi Kuroki (Kyoto University). They told the 'story of us', how the field of regenerative rehabilitation has evolved, and how Kyoto University became a co-host with the University of Pittsburgh for the 2017 symposium.

Conference keynote speaker, David J Mooney (Harvard University, MA, USA), provided an insightful talk entitled 'Exploiting mechanics to promote regeneration'. 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 immunoprotection during delivery [2].

The theme for the first session centered on applied mechanobiology. The unique and complex integration of appropriate forces with adequate biochemical factors required for musculoskeletal tissue regeneration were highlighted. Adam Feinberg (Carnegie Mellon University, PA, USA) discussed how muscle tissue organizes itself in his presentation, 'Advanced biofabrication strategies for engineering 3D muscle tissue' [3]. Thomas A Rando (Stanford University, CA, USA), presented a talk entitled 'Regenerative rehabilitation therapy for volumetric muscle loss'. His findings suggest implanting or injecting some nonmuscle cells into the region of volumetric muscle loss may improve regeneration since muscle is composed of various cell types [4]. Martin Stoddart (AO Research Institute, 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* [5].

The second session ushered in concepts surrounding the theme of neurologic applications of regenerative rehabilitation. Attendees gained an overview of the role of environmental cues and forces, as well as rehabilitative techniques, for optimizing cell-based therapies for neurological deficits. In his presentation entitled 'Clinical trials of stem cell transplantation for treatment of stroke', Lawrence R Wechsler (UPitt) summarized poststroke sequelae, and highlighted the importance of homing factors. He emphasized the importance of local delivery of regenerative therapies in the context of chronic stroke, due to the absence of homing factors that are capable of attracting cells delivered systemically [6]. In a talk entitled 'Clinical and neurophysiological evidences of brain plasticity', Carmelo Chisari (University Hospital of Pisa, Italy) talked about the benefits of aerobic exercise and transcranial magnetic stimulation poststroke [7]. George Kraft (University of Washington, WA, USA) presented data from a clinical trial on patients with multiple sclerosis in his talk, 'The use of autologous stem cells in rehabilitation of multiple sclerosis'. *Post hoc* investigation suggested that the irradiation that patients received prior to $CD34^+$ cell therapy might have caused direct damage to the spinal cord, thus reducing the potential for positive outcomes [8].

An evening poster session and networking reception followed. Poster award winners were: first place, Hikaru Mamiya (UPitt), 'Biomechanical signal may inhibit klotho expression'; second place, W Michael Southern (University of Georgia, GA, USA), 'Mitochondrial targeted therapy for dystrophic mice'; and third place, Jr-Jiun Liou (UPitt), 'Platelet rich plasma for cartilage repair'. The evening ended with a special session panel discussion entitled 'Glories, gripes and grapes'. Panelists included: Esther E Dupont-Versteegden (University of Kentucky, KY, USA), G Kelly Fitzgerald (UPitt), Ralph Nitkin (National Institute of Child Health and Human Development, USA) and Kimberly Topp (University of California, CA, USA). Take home messages from this hearty discussion 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.

The theme of the final session of the symposium was entitled 'Translate your science: regenerative rehabilitation technologies, methods and approaches'. An appreciation of how cellular and technological advances are being used in combination with rehabilitation approaches to both assess and enhance regenerative rehabilitation outcomes was gained. Ryosuke Ikeguchi (Kyoto University Graduate School of Medicine, Kyoto, Japan) gave an excellent overview on 'Rehabilitation and regeneration of peripheral nerve injury', indicating that collectively, findings suggest that nerve repair or transplant in combination with appropriate exercise leads to optimized outcomes. Koichi Nakayama (Saga University, Japan) gave a talk entitled 'Introduction of scaffold-free bio 3D printer for organ regeneration', illustrating 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 [9]. Robert Gaunt (UPitt) discussed his work in a talk on 'Human brain–computer interfaces for sensorimotor science and rehabilitation'. For brain–computer

interfaces to work well, it must properly isolate, acquire and translate neural information, and utilize those neural signals to produce movement or perceive sensation [10]. In closing, James J Irrgang (UPItt) provided a schematic overview of suitable outcome measures for regenerative rehabilitation research that correspond to the International Classification of Functioning model.

Postsymposium regenerative rehabilitation research workshops were offered for the first time at this conference. The two concurrent workshops were: 'Clinical study design for regenerative rehabilitation', facilitated by Marcas Bamman (University of Alabama, AL, USA) and 'Rehabilitation strategies in preclinical models: an overview of the fundamentals', led by Linda Noble-Haeusslein (University of Texas, TX, USA) and Gordon L Warren, III (Georgia State University, GA, USA). Both of 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.

Closing remarks at the symposium, by Dr Ambrosio, reinforced the impetus for efforts in regenerative rehabilitation, 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. Educators were urged to incorporate regenerative rehabilitation content into curricula, and for clinicians and scientists to interact closely to move the field forward. The 7th Annual International Symposium on Regenerative Rehabilitation will be hosted at the University of Washington, 11–13 October 2018, in the beautiful city of Seattle. All are welcomed.

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Conference details

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References

1 Kochanek PM, Bramlett HM, Shear DA *et al.* Synthesis of findings, current investigations, and future directions: operation brain trauma therapy. *J. Neurotrauma* 33(6), 606–614 (2016).

2 Vining KH, Mooney DJ. Mechanical forces direct stem cell behaviour in development and regeneration. *Nat. Rev. Mol. Cell Biol.* 18(12), 728–742 (2017).

3 Duffy RM, Sun Y, Feinberg AW. Understanding the role of ECM protein composition and geometric micropatterning for engineering human skeletal muscle. *Ann. Biomed. Eng.* 44(6), 2076–2089 (2016).

4 Quarta M, Cromie M, Chacon R *et al.* Bioengineered constructs combined with exercise enhance stem cell-mediated treatment of volumetric muscle loss. *Nat. Commun.* 20(8), 15613 (2017).

5 Fahy N, Alini M, Stoddart MJ. Mechanical stimulation of mesenchymal stem cells: Implications for cartilage tissue engineering. *J. Orthop. Res.* 36(1), 52–63 (2018).

6 Hess DC, Wechsler LR, Clark WM *et al.* Safety and efficacy of multipotent adult progenitor cells in acute ishaemic stroke (MASTERS): a randomized, double-blind, placebo-controlled, Phase II trial. *Lancet Neurol.* 16(5), 360–368 (2017).

7 Bertolucci F, Chisari C, Fergni F. The potential dual role of transcallosal inhibition in post-stroke motor recovery. *Restor. Neurol. Neurosci.* 36(1), 83–97 (2018).

8 Nash RA, Hutton GJ, Racke MK *et al.* High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for relapsing-remitting multiple sclerosis (HALT-MS): a 3-year interim report. *JAMA Neurol.* 72(2), 159–169 (2015).

9 Toratani T, Nakase J, Numata H *et al.* Scaffold-free tissue-engineered allogenic adipose-derived stem cells promote meniscus healing. *Arthroscopy* 33(2), 346–354 (2017).

10 Flesher SN, Collinger JL, Foldes ST *et al.* Intracortical microstimulation of human somatosensory cortex. *Sci. Transl. Med.* 19(8), 361ra141 (2016).