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Emergent themes from Second Annual Symposium on Regenerative Rehabilitation, Pittsburgh, Pennsylvania

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INTRODUCTION

Regenerative medicine advances hold the potential to drive dramatic progress in the prevention and treatment of individuals with a host of acute and chronic pathologies. Regenerative medicine is "an interdisciplinary field of research and clinical applications focused on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including congenital defects, disease, trauma and ageing" [1]. With return to normal activities of daily living as the ultimate goal of these biological therapies, it is clear that regenerative medicine is tightly intertwined with rehabilitation, which also involves the optimization of function and performance. As regenerative medicine approaches increasingly permeate medical practice, important questions arise about the development of adjunct clinical protocols that will maximize the therapeutic benefit of these technologies: Does the initiation of rehabilitation protocols following transplantation of biological scaffolds or cells enhance or hinder functional

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efficacy of the technology? If a rehabilitation protocol is initiated following administration of a biological therapy, as is likely to occur in a clinical setting, what is the optimal timing and dosing? Finally, how can basic science discoveries be most efficiently translated such that they may guide the development of targeted rehabilitation programs to promote tissue healing?

THEORETICAL PREMISE FOR REGENERATIVE REHABILITATION

It is increasingly recognized that mechanotransduction, or the conversion of a mechanical stimulus to chemical activity, plays an important role in dictating molecular, cellular, and tissue responses. Mechanotransductive pathways may be initiated by stretch, exercise, or electrical stimulation, indicating that the application of rehabilitation could dictate stem cell behavior and, as such, tissue regenerative potential. There is mounting evidence to suggest that, like endogenous stem cells, donor stem cells are amenable to the influences of the dynamic microenvironment [2–5]. The time is right to better understand the potential synergy between rehabilitation and the development of biological therapies. Such an understanding should clearly be rooted in collaborative investigations at the early stages of technology conceptualization and development so that the transition to the clinic may be smooth and efficient [6].

Regenerative rehabilitation may be defined as the integration of principles and approaches in rehabilitation and regenerative medicine with the ultimate goal of developing innovative and effective methods that promote the restoration of function through tissue regeneration and repair. While interdisciplinary research and practice is desirable, few opportunities are available to bring together scientists and clinicians working in these two disparate fields. With this in mind, the Second Annual Symposium on Regenerative Rehabilitation, organized by the University of Pittsburgh Medical Center Rehabilitation Institute; the McGowan Institute for Regenerative Medicine; the School of Health and Rehabilitation Sciences at the University of Pittsburgh; and the Palo Alto Department of Veterans Affairs (VA) Rehabilitation Research and Development Center for Tissue Repair, Regeneration, and Restoration, was held on November 12–13, 2012, in Pittsburgh, Pennsylvania. The regenerative rehabilitation symposium was designed to cross disciplinary boundaries in order to create a unique forum where stakeholders in the field of regenerative medicine could interact with rehabilitation clinicians and scientists to discuss the current and future landscape of the field. The specific objectives of the 2012 event, as summarized in this editorial, were (1) to catalyze the development of novel interactions and research directions among researchers, clinicians, and students conducting research in regenerative medicine and/or rehabilitation; (2) to determine barriers in the development of regenerative rehabilitation approaches; (3) to identify practical methods to overcome existing barriers; and (4) to introduce the concept of regenerative rehabilitation to graduate students, medical students, and medical residents in the rehabilitation field with the goal of inspiring the next generation of clinicians and scientists to embrace innovative technologies and to incorporate those technologies in their nascent clinical practices and research programs.

REGENERATIVE REHABILITATION FOR NEUROLOGICAL APPLICATIONS

In his opening remarks, Dr. Steven Wolf (Emory University) drew attention to the fact that, as of January 2, 2013, 14,084 articles could be identified under a PubMed search using "regenerative medicine" as the sole search term. Of that number, 13,366 (94.9%) have been published since the year 2000. Within this categorization, 282 were identified as "regenerative rehabilitation," a subset within regenerative medicine. When segmented by time intervals (Table), the number of articles appearing between 2010 and 2012 almost equals the total number cited between 2005 and 2010, and both represent a substantial increase from all previous years. Among the diagnostic categories in which regenerative rehabilitation was identified, 28 articles addressed spinal cord injury, 16 stroke survivors, and 3 individuals with multiple sclerosis. However, a more detailed analysis of these articles reveals that 184/282 (65.2%) examined animal models, several did not meet the definition noted previously, and often the translational articles were conceptual rather than interventional or explorative.

Among articles categorized as "regenerative rehabilitation" following stroke as an example, several [7–10] addressed the role of robotics in improving upper-limb function, an approach that is more closely aligned with bioengineering interventions than with regenerative rehabilitation. Other articles began to explore serum levels as they correlated with functional changes but did not speak to interventions that could improve this correlation. For example, in reviewing 407 patients poststroke, Åberg et al. observed that high serum insulin-like growth factor-I (IGF-I) levels during 3 mo of rehabilitation following stroke correlated better with long-term recovery as measured by the modified Rankin scale [11]. This finding invites the question of how such levels can be best augmented given that IGF-I exerts a neuroprotective and regenerative effect in experimental models of stroke. The potential application of stem cell therapy [12] in combination with neurorehabilitative therapies will require assurances regarding the efficacy of designated cells, routes of delivery, and distribution and modes of action.

Therapeutic interventions may facilitate release of brain-derived neurotrophic factor (BDNF) near the area of infarct, the appropriate timing of AMPA receptor activation with the concomitant mediation of BDNF release [13], the timing of pharmacological agents that affect release of glutamate and GABA neurotransmitters [14], and the fostering of neurogenesis and axonal sprouting along with blood vessel remodeling [15]. Determining the extent to which these considerations can be individually or collectively integrated with existing or novel neurorehabilitative approaches known to induce plasticity within the central nervous system [16] will form one of several critical cornerstones for regenerative rehabilitation applications among patients with specific neuropathologies, such as stroke.

In a plenary session entitled "Spinal Cord Injury and Regenerative Rehabilitation," Drs. Paul Reier and Heather Ross (University of Florida) countered the dogma that lesions of the central nervous system are "fixed" and that "nothing may be regenerated." While both rehabilitation and regenerative medicine strategies are being pursued to address the tissue damage seen following central nervous system injury, in isolation, these strategies are currently limited by technical hurdles and inconsistent biological outcomes. Work from Dr.

Ross's laboratory is currently laying the groundwork to use interventions such as intermittent hypoxia as a physical therapist-administered therapy to complement cell replacement. The goal of such systemic therapy is to condition not only the transplanted cells but also the injured environment. Future work will systematically investigate the beneficial effect of this combination therapy approach in a preclinical model.

CONVERGING THEMES IN REHABILITATION, REGENERATIVE MEDICINE, AND DEVELOPMENT OF INNOVATIVE TECHNOLOGIES

Neuroprosthetics (NPs) is a burgeoning field that involves interfacing directly with the nervous systems as a means of replacing lost function. An example of a clinically available NP is the cochlear implant. NPs have great potential to complement the field of regenerative rehabilitation. Research has demonstrated that the environment and stimulation are critical to appropriate differentiation of stem cells. For example, Distefano et al. found that muscle-derived stem cells are more likely to differentiate into muscle and demonstrate increased functional contributions when exposed to neuromuscular electrical stimulation [17].

In their session, Drs. Michael Boninger and Elizabeth Tyler-Kabara (University of Pittsburgh) described the bench-to-bedside research trajectory of using thoughts to control robotic arms through brain-computer interface technology. In the central nervous system, it may be argued that brain-computer interfaces could stimulate appropriate stem cell differentiation to maximize plasticity. Recent work has shown high degree-of-freedom control of a prosthetic limb with two types of brain-computer interfaces [18–19]. The ability to decode electrical signals and potentially stimulate through the same interface offers promise in the field of stroke, where it is likely that a combination of stem cells and some form of stimulation would be required to repair large lesions. This represents an exciting potential area for future investigations.

As presented by Dr. Ravi Bellamkonda (Georgia Institute of Technology), a more direct example is provided by microchannel electrodes that are capable of recording and stimulating nerves and can also provide a matrix to allow for nerves to regrow across an injury [20]. The convergence of the NPs and interfaces with biologic regenerative medicine applications should offer exciting future possibilities for individuals with disabilities.

IMPORTANCE OF REGENERATIVE REHABILITATION IN TREATMENT OF MUSCULOSKELETAL DISORDERS

The presentations of Drs. Scott Rodeo (Hospital for Special Surgery) and Richard Shields (University of Iowa) had broad conceptual overlap related to regenerative rehabilitation for musculoskeletal applications, but used very different models and approaches. The symposium keynote speaker, Dr. Rodeo, explained the advances in our understanding of the basic biology of musculoskeletal tissues. He wove into his presentation key advances from diverse fields such as biomaterials, stem cell biology, molecular biology, tissue engineering, and genetics. Specifically, Dr. Rodeo presented outcomes related to cellular therapies directed at healing acute articular cartilage defects by using cartilage autograft implantation techniques, hyaluronic acid-based degradable scaffolds with chondrocytes, and mesenchymal stem cells. He explained that the primary goal of these therapies is to develop a stable chondrocyte phenotype. The challenge is to direct these implanted cells to proliferate and differentiate into normal articular cartilage. Equally challenging is the chondrocytic matrix that often has inferior mechanical properties from the normal chondrocyte phenotype. The strategic use of growth factors and cytokines, through platelet-rich plasma techniques, offers one contemporary strategy to guide chondrogenic differentiation of cells. Using a careful review of the literature, Dr. Rodeo articulated the scientific basis for tendon healing through the use of stem cells. He concluded that the extent to which platelet-rich plasma influences tendon healing remains debatable and appears highly dependent on the specific composition of the platelet-rich plasma. More work in this field among several disciplines, including rehabilitation specialists, will be essential to developing successful cellular outcomes.

Dr. Shields presented work demonstrating the capacity for muscle and bone tissues to respond to purely mechanical stresses in humans with paralysis. His intervention to trigger tissue adaptation was derived from muscle contractions induced by computer-generated electrical stimulation or a servo-controlled vibratory stimulus through a custom designed device. The novelty of his work is that his outcome measurements span from bench to bedside. His studies on human paralyzed muscle provide key hints about the power of appropriately dosed muscle and bone stress in human tissues. By analyzing gene regulation, he provides the first line of evidence about the acute and chronic effect of mechanical stresses through exercise on human tissue health. He shared new findings that show gene regulation is modulated specifically by the frequency of the electrical stimulation of muscle and dose of muscle force produced by the electrical stimulation. He also emphasized that muscle gene regulation during passive mechanical vibration, while extensive, invokes an entirely different subpopulation of genes, supporting that future regenerative rehabilitation strategies will need to be specific to the ultimate goal of the desired tissue outcome.

His long-term training studies of a single limb, while using the opposite limb as a control, indicated how powerful a routine and timely dose of activity is on muscle and bone plasticity over several years. Importantly, the adaptations were functional as the muscle transforms from a fast fatigable phenotype to a fatigue resistant phenotype. Noteworthy was the dramatic influence the muscle training had on tibia bone mineral density and preservation of trabecular architecture, effects only observed in the limbs that received the electrical stimulation training. Dr. Shields emphasized that, from his studies, we may glean some key insights into how to optimally stress other musculoskeletal tissues that receive cellular therapies to promote tissue regeneration and repair.

LESSONS LEARNED FROM REGENERATIVE REHABILITATION IN MILITARY MEDICINE

Military medicine extends from the earliest stages of combat-related injuries to the subacute and chronic phases of rehabilitation of soldiers with severe debilitating injuries. The presentations in the "Regenerative Rehabilitation in Military Medicine" session sought to highlight current approaches to regenerative rehabilitation within the context of combat injuries. Dr. Thomas Rando (Stanford University) discussed the focus of the Center for

Tissue Regeneration, Repair, and Restoration at the VA Palo Alto Healthcare System, which is dedicated to bridging regenerative biology, materials science, and rehabilitative interventions. Using a mouse model of volumetric muscle loss (VML) to mimic the kinds of patients seen at the VA following combat-related trauma to limbs, researchers at the center are exploring the potential for muscle stem cell transplantation to promote healthy muscle regeneration even in the chronic setting. The use of specially designed biological scaffolds to enhance the effectiveness of the transplanted cells is combined with state-of-the-art stem cell isolation and maintenance, all integrated into rehabilitative strategies to promote muscle repair restoration. Dr. Thomas Walters discussed research at the U.S. Army Institute of Surgical Research in San Antonio on the issue of limb salvage versus amputation in the setting of severe injuries. Toward the goal of limb salvage, Dr. Walters discussed adaptive responses of the uninjured portion of muscle also in a model of VML. Interestingly, it appears that adaptations in the setting of physical therapy may contribute significantly to improved function, and these findings were discussed in terms of the relationship to potential tissue engineering/regenerative medicine interventions, highlighting the importance of an integrated approach. Dr. Paul Pasquina discussed ongoing research at Walter Reed National Medical Center on the spectrum of complex traumatic injuries sustained by soldiers, particularly in Iraq and Afghanistan, with an emphasis on injuries to limbs, brain, and spinal cord. Within each of these areas, he discussed the role of rehabilitation integrated into research in regenerative medicine, prosthetics, and robotics and the continuum of care from the battlefield to civilian life or the return to Active Duty. Finally, Dr. John Dudley Malone discussed the role of the Naval Medical Center in San Diego in managing the care and rehabilitation of servicemen and women who sustain combat-related injuries. In addition to collaborations with the Intrepid Centers of Excellence in San Antonio and Bethesda, Dr. Malone described the mission of the Armed Forces Institute of Regenerative Medicine, which actively promotes collaborations between military and civilian investigators.

Following the formal presentations, Dr. Rando moderated a question and answer session to allow members of the audience to ask specific questions of panel members and to offer their own experience or perspective on how the lessons learned from military and civilian regenerative rehabilitation might be mutually beneficial in terms of unique challenges and shared experiences. During this session, panelists shared the importance of “early buy-in” from clinicians, military and civilian, to facilitate the translation of cutting-edge laboratory developments into positive changes in medical practice. Dr. Walters emphasized that the rapid and aggressive progress in the areas of regenerative medicine and rehabilitation that has taken place in military medicine over the past 10 years is largely the result of desperation. Never before in history has the military been faced with the level of medical challenges that it is facing now, which arguably has led to implementing treatments that would never have been attempted under peacetime conditions, and more importantly, never in the (litigious) environment of civilian medicine. As the war winds down, we still have much to learn from the aggressive protocols that have been implemented in the military during these times of desperation, further highlighting the need for civilian-military collaborative efforts. As emphasized by Dr. Malone, critical factors to fostering such collaborations include adequate financial support to overcome geographic barriers and, more importantly, a firm foundation based on trust—trust with data sharing, publications, and financial matters.

IMPLICATIONS OF REGENERATIVE REHABILITATION IN EDUCATIONAL PROGRAMS

As highlighted in the "Regenerative Rehabilitation in Education" session (presented by Drs. Joel Stein [Columbia University] and Anthony Delitto [University of Pittsburgh]), integrating up-to-date basic and applied information is always a challenge in any professional education program. It is particularly challenging to introduce and integrate new and innovative material such as that in the regenerative rehabilitation area across the 200+ professional physical therapy programs. Using the *Guide for Physical Therapy Practice*'s general categorization of patient management (Musculoskeletal, Neuromuscular, Cardiopulmonary, and Integumentary), Dr. Delitto discussed the development of a standardized model curriculum in regenerative rehabilitation in which contributions in germane areas should be sought from renowned experts and placed in a repository that can be shared through tele-educational methods. Suggestions of how to integrate this material in each area of practice were also discussed and are summarized as follows:

1. Create a centralized open-access repository of lectures in each of the major categorizations of physical therapy and rehabilitation medicine practice. Lecture contributions should be solicited from leading international authorities.

2. Initiate a dialog with educational representatives (e.g., Academic Council, American Physical Therapy Association, Association for Academic Physiatrists) with the goal of identifying critical aspects of regenerative rehabilitation that should be incorporated into entry-level professional didactic curricula.

3. Explore the feasibility of creating short- and long-term research experiences for entry-level professional students within established regenerative rehabilitation centers.

The National Institutes of Health has also recognized the increasing need to expose students, residents, and junior investigators to the emerging field of regenerative rehabilitation. R13 conference grant funds generously provided from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Institute of Arthritis and Musculoskeletal and Skin Disorders, the National Institute of Biomedical Imaging and Bioengineering, and the National Institute of Neurological Disorders and Stroke made possible the distribution of 17 domestic and 3 international trainee/young investigator travel awards to attend the 2012 symposium.

CONCLUSIONS

The proposed integration of the fields of regenerative medicine and rehabilitation has relevance to a broad scope of research interests and clinical specialties. Scientists in the field of regenerative medicine stand to benefit from increased incorporation of functional outcomes assessment when determining the therapeutic benefit of biological technologies being investigated. Moreover, the application of clinically relevant and cost-effective approaches to elicit targeted and specific physiological responses may be an effective means to maximize efficacy and, ultimately, hasten the translation of these technologies into medical practice. Accordingly, as our understanding of mechanisms underlying tissue regeneration following injury, disease, and aging progresses, rehabilitation specialists will benefit from the continued incorporation of these emerging principles into the design of clinical protocols.

The annual Regenerative Rehabilitation Symposia series is a unique opportunity for students, researchers, and clinicians working in the interrelated fields of regenerative medicine and rehabilitation to meet, exchange ideas, and generate new collaborations and clinical research questions. For additional information regarding this symposium series, including updates regarding the next event, which will be held on April 10-11, 2014 in San Francisco, California, please visit www.mcgowan.pitt.edu.

Biography

Left to right: Fabrisia Ambrosio, PhD, PT; Michael L. Boninger, MD; Clifford E. Brubaker, PhD; Anthony Delitto, PhD, PT, FAPTA; William R. Wagner, PhD; Richard K. Shields, PT, PhD, FAPTA; Steven L. Wolf, PhD, PT, PAFTA, FAHA; Thomas A. Rando, MD, PhD

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Table

Historical antecedents: PubMed search November 5, 2012.

Search Term	Years	Articles Found (*n*)
Regenerative Medicine		
	1920s	1
	1960s	2
	1970s	1
	1985–1989	93
	1990–2012	13,545
	Total	13,642
Regenerative Rehabilitation		
	1970s	2
	1980s	2
	1990s	23
	2000–2010	120
	2010–2012	135
	Total	282