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Regenerative Rehabilitation – a New Future?

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Abstract

Modern rehabilitation medicine is propelled by newfound knowledge aimed at offering solutions for an increasingly aging population afflicted by chronic debilitating conditions. Considered a core component of future healthcare, the roll-out of regenerative medicine underscores a paradigm shift in patient management targeted at restoring physiologic function and restituting normative impact. Nascent regenerative technologies offer unprecedented prospects in achieving repair of degenerated, diseased or damaged tissues. In this context, principles of regenerative science are increasingly integrated in rehabilitation practices as illustrated in the present Supplement. Encompassing a growing multidisciplinary domain, the emergent era of “regenerative rehabilitation” brings radical innovations at the forefront of healthcare blueprints.

Regenerative medicine: An introduction

Regenerative medicine encompasses the "process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects".¹ This new field holds the unprecedented promise of regenerating tissues and organs in the body by either replacing damaged tissue or by promoting the body's own repair mechanisms to heal previously irreparable conditions. As regenerative medicine becomes increasingly integrated into medical practice, new approaches will address the root cause of disease and offer previously unachievable prospects for tissue repair. Regenerative medicine largely draws from the field of transplantation medicine, that together with implantable medical devices, has profoundly altered the trajectory for chronic patients suffering from end-stage organ failure.² However, transplantation medicine is limited by donor organ shortage. The US Department of Health and Human Services Organ Procurement and Transplantation Network cites a waiting list for all organs in excess of 120,000 patients at any given time.³ In the USA annually around 30,000 patients received transplanted organs as part of a standard of practice.⁴ But, the gap between available organ donation and recipients is rapidly widening. Moreover, recipients, although fortunate to receive donor organs, are placed at risk for tissue rejection and must receive life-long immunosuppressive drug therapy with an increased incidence of transplantation-associated cancers. Furthermore, transplant complications are common.^{5–8} Lung transplant recipients, for example,

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experience the highest rates of re-hospitalization for transplant complications, i.e., ~44 per 100 patients within the first year.⁹ Together, these data indicate that transplantation needs far exceed supply, and even when transplanted organs are available, patients face life-long challenges.

The emerging field of regenerative medicine aims to address the unmet medical need for organ and tissue replacement. Regenerative medicine cover a broad spectrum including methods for promotion of self-healing, cell-based therapies, tissue engineering and neo-organogenesis. Indeed, the world's first successful laboratory-grown organ (a urinary bladder) was generated from the patient's own cells, shaped by a bioreactor and subsequently surgically implanted back into the patient.^{10–15} Atala and colleagues created engineered bladder tissues by seeding autologous urothelial and muscle cells onto collagen-polyglycolic acid scaffolds. After 7 weeks of culture in laboratory bioreactors, the autologous engineered bladders were used in a surgical reconstruction for myelomeningocele patients.^{10–15} Long-term follow-up in patients treated by this regenerative technique demonstrated improvement in bladder leak point pressure, volume and compliance. This proof-of-concept technology provides an early example of the upcoming era of regenerative solutions^{10–15}.

A few examples of regenerative medicine technologies already tested in patients are presented in Table 1. A wide array of engineered organs (urinary bladder,^{10–15} trachea,^{16,17} cornea^{18–20}) or tissues (skin,^{21–24} cartilage,^{25–29} muscle^{30–32}) are developed to the point of clinical applications. Many other regenerative technologies are under development in preclinical stages prior to human trials. For example, a recent breakthrough reported in the journal *Nature* from the laboratory of Murry and colleagues described the differentiation into cardiomyocytes of human embryonic stem cells (hESCs) to regenerate damaged heart tissue in non-human primates.³³ Investigators injected 1 billion heart muscle cells derived from hESCs into the infarcted muscle of pigtail macaques. The group found that over subsequent weeks, the stem-cell derived heart muscle cells infiltrated into the damaged heart tissue, then matured, assembled into muscle fibers, and began to beat in synchrony with the macaque heart cells. After three months, the cells appeared to have fully integrated into the macaque heart. Future efforts by this group will work to reduce the risk of complications including arrhythmias.

Supported by pre-clinical experience, cardiovascular regenerative therapies are increasingly evaluated in clinical trials. Trial results across studies show feasibility and safety of adult stem cells, although efficacy outcomes remain variable at least with first generation cell platforms³⁴. Next generation regenerative products with an upgraded therapeutic potential are thus being developed. This includes the first human lineage-specified cardioreparative stem cell phenotype tested in advanced clinical trials³⁵

Regenerative medicine in practice

The notion of a “regenerative medicine clinic” has been formulated as a centralized portal to existing regenerative services, facilitating enrollment into clinical protocols³⁶. Mayo Clinic, for example, has launched a prototypic consult service for regenerative medicine and

surgery set as a singular point of access. The “Regenerative Medicine Consult Service” at Mayo Clinic offers opinion on the risks and benefits of a regenerative approach and addresses available products or services³⁷. Systems and procedures in place enable the regenerative consult service to participate in ongoing care plans, and to be offered as an e-consult option.

Regenerative rehabilitation

The central goal of “regenerative rehabilitation” is to restore normal function. Spanning use of cell, pharmacological and bioengineering technologies, along with physical modalities and exercise, regenerative and rehabilitation medicine are “tightly intertwined” as underscored by Ambrosio and colleagues.³⁸ In this Supplement to the *American Journal of Physical Medicine and Rehabilitation*, leading faculty at rehabilitation medicine programs across the country highlight examples of regenerative technologies under development or in current practice in rehabilitation disciplines.

Between the covers

Gentile et al[link to AJ14126S] provide an example of how rehabilitation modalities fit into a regenerative approach in a limb trauma patient who received muscle cell transplantation onto a bioengineered scaffold. In this case study, a rehabilitation program was directed to optimize post transplantation recovery in support of the idea that exercise and mechanical stimulation play a role in the success of musculoskeletal regeneration. This clinical example of “regenerative rehabilitation” provides a framework for a working definition of a hybrid discipline still in infancy. Jasuja and LeBrasseur [link to AJ14033s] describe the use of promising biological and small molecule interventions in development for skeletal muscle regeneration. The authors discuss how new pharmacological agents, such as selective androgen receptor modulators (SARMs) and myostatin inhibitors, might offset age- and disease-associated muscle wasting. Bruan et al [link to AJ14090S] discuss how gene replacement therapy using adeno-associated virus (AAV) offers new hope for patients suffering from neurodegenerative muscle disorders, such as Duchenne muscular dystrophy and a rare inherited muscle disease, X-linked myotubular myopathy. Pourcho et al [link to AJ13548S] describe how platelet-rich plasma may regenerate damaged tissue in the knees of patients with osteoarthritis, and discuss recommendations for clinical use. The use of stem cells to regenerate the intervertebral disc (Gou et al [link to AJ14130S]) or to regenerate cells of the nervous system (Maldonado-Soto et al [link to AJ14087S]) is under active investigation in rehabilitation medicine laboratories. Bioengineering, robotics and stem cells may provide synergy when coupled together with regenerative rehabilitation strategies described by Boninger et al [link to AJ14031S]. Stem cells are also under study as biological reagents to model inherited diseases using genetic reprogramming (Mack et al, [link to AJ14091S]). Finally, Behfar et al [AJ14033S] discuss how regenerative medicine technologies enhance cardiac rehabilitation.

A definition for regenerative rehabilitation

To address functional impairment in a patient, the following working definition for the emerging field of regenerative rehabilitation is here proposed:

“Regenerative rehabilitation integrates regenerative technologies with rehabilitation clinical practices to reconstitute function and quality of life in individuals with disabilities due to otherwise irreparable tissues or organs damaged by disease or trauma”.

A similar definition can be found online at the American Physical Therapy Association (APTA) website: “Regenerative Rehabilitation is the integration of principles and approaches from 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”.³⁹ Whether regenerative rehabilitation includes the use of emerging technologies such as stem cell transplantation or includes aspects of new knowledge gained from a better understanding of physiological processes affected by mechanotransduction or neural recruitment is part of a continuum of innovation. Regardless, the power of combining emerging technologies and new knowledge in both disciplines could be transformative for patients with previously untreatable disorders or injuries.

Integrating regenerative medicine into an academic rehabilitation program

Regenerative rehabilitation was first formalized into an academic rehabilitation department at New York’s Columbia University. The first combined department of Rehabilitation and Regenerative Medicine⁴⁰ led by Dr. Joel Stein, administers the Columbia Stem Cell Initiative and serves to conduct original stem cell research and bring together members of the diverse stem cell community within the university under a common umbrella. More than 100 stem cell laboratories are highlighted by the Initiative’s website and concurrent education, training and research programs are hosted by the same administrative organization. Dr. Christopher Henderson, whose primary faculty appointment is in the Rehabilitation and Regenerative Medicine department, directs the stem cell initiative at Columbia. Combining rehabilitation medicine with stem cell research in the same departmental structure opens up unique and forward looking opportunities to expand the scientific basis of rehabilitation medicine. The Physical Medicine and Rehabilitation Department at Mayo Clinic recently launched the Rehabilitation Medicine Research Center directed by Dr. Christopher Evans. A central priority of this comprehensive center is the development of multidisciplinary programs, spanning the discovery-translation continuum, within the Regenerative Rehabilitation Medicine portfolio under the guidance of Dr. Jay Smith and the Mayo Clinic Center for Regenerative Medicine, a catalyst in advancing rigorous new knowledge on disease causes and cures into informed delivery of quality care. Other departments throughout the US are also integrating regenerative technologies into rehabilitation departments through close collaboration with regenerative medicine institutes. For example, the faculty at the McGowan Institute for Regenerative Medicine at the University of Pittsburgh collaborate with rehabilitation scientists in the Department of Rehabilitation Medicine on projects ranging from skeletal muscle regeneration to brain-computer interfaces. Another example is seen at the University of Washington’s Institute for Stem Cell and Regenerative Medicine (ISCRM) where faculty in the Department of Rehabilitation Medicine find their primary bench laboratory space. Both gene therapy and stem cell projects are underway by rehabilitation scientists working in the laboratory space at ISCRM.

Future steps

The ultimate goal is to integrate regenerative medicine into rehabilitation medicine departments. For this purpose, the creation of educational symposium to disseminate new knowledge and information about regenerative medicine technologies, networking activities and collaborative opportunities are essential. Working groups and consortium with the participation of scientists, rehabilitation clinicians and physical therapists involved in the areas of regeneration and rehabilitation are of critical importance. In this regard, The University of Pittsburg together with other rehabilitation centers in U.S.A. are pioneering highly interactive educational activities in which individuals working in the fields of regeneration and rehabilitation medicine, met to discuss “principles of regenerative medicine and how rehabilitation interfaces with these state-of-the-art technologies for optimal patient recovery”. This annual meeting is one of the first steps formally established to disseminate information, and create networking activities with the ultimate goal to create a discovery-translation-application roadmap for the express purpose of science-supported practice advancement that will drive the field of regenerative rehabilitation medicine.

In addition, each rehabilitation center in academic institution should create multidisciplinary working groups that include rehabilitation faculties, to identify activities in their academic institutions that could be defined as regenerative rehabilitation. This is the case at the University of Washington; where a steering committee led by Dr. Martin Childers has created a vision and mission statement that provide guidance for future decision-making about structuring regenerative rehabilitation activities:

Vision: To create and implement novel regenerative technologies to improve function and quality of life in individuals with disabilities.

Mission: To develop innovative trans-disciplinary research, educational and clinical programs to advance the frontiers of regenerative rehabilitation by leveraging gene and cell therapy, bioengineering, and clinical discoveries

The steering committee met regularly to address opportunities for collaboration and to explore ways to begin a program in regenerative rehabilitation. To measure rehabilitation activities aligned with “regenerative medicine,” a simple poll was sent out to about 100 faculty members. To explore opportunities for future collaboration between rehabilitation medicine and faculty actively engaged in regenerative medicine, a recurring open forum (social event or seminar) was recommended.

To expand research and training activities in regenerative medicine into future rehabilitation programs, grants opportunities at federal level as well as private organization/foundations need to be identified and if nonexistent, to be created and supported. Regenerative medicine curriculum should be added to Physical Medicine and Rehabilitation training programs including medical residency, fellowship and therapies program.

In summary, Regenerative medicine constitute an emerging field focused on the repair and functional restoration of organs damaged from diseases, trauma and degenerative conditions

and it is built to represent the future of medical care. Understanding the principles of regenerative medicine is essential and incorporate them into rehabilitation medicine is critical in order to drive validated science into clinical options that will allow us to build a model of care that have the potential to change a letter in the word CARE to transform it in CURE. In this supplement the readers will find many examples of translation of regenerative rehabilitation principles into clinical practice. We expect that this supplement represent one of the multiple initiatives to contribute to the further developing of the field of regenerative rehabilitation medicine.

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Table 1

Regenerative medicine technologies applied to patient

Engineered organ or tissue	Types of cells used	Scaffold	Reference
Skin	Epithelial or none	Complex; multiple in use	Gunter et al, 2012
Urinary bladder	Urothelial, muscle	Collagen; collagen/polyglycolic acid	Atala et al, 2006
Trachea	Epithelial, chondrocytes	Cadaver trachea	Wise et al, 2013; Berg et al, 2014
Cartilage	Mesenchymal stem cells, others	None	Pastides et al 2013 (review)
Cornea	Limbal stem cells	Amniotic membrane	Kruse et al, 2008
Muscle	None	Porcine intestine submucosa	Mase et al, 2010
Heart	Neonatal cardiac cells	Decellularized whole rat heart	Ott et al, 2008