Regenerative Rehabilitation

A New Future?

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 health care, the rollout 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.

Key Words: Regenerative Medicine, Technology, Rehabilitation

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.” This new field holds the unprecedented promise of regenerating tissues and organs in the body by either replacing damaged tissue or 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 experiencing end-stage organ failure. However, transplantation medicine is limited by donor organ shortage. The U.S. 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. In the United States annually, around 30,000 patients received transplanted organs as part of a standard of practice. However, 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 lifelong immunosuppressive drug therapy with an increased incidence of transplantation-associated cancers. Furthermore, transplant complications are common.
Transplant recipients, for example, experience the highest rates of rehospitalization for transplant complications, that is, approximately 44 per 100 patients within the first year. Together, these data indicate that transplantation needs far exceed supply, and even when transplanted organs are available, patients face lifelong challenges.

The emerging field of regenerative medicine aims to address the unmet medical need for organ and tissue replacement. Regenerative medicine covers 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. Atala and colleagues created engineered bladder tissues by seeding autologous urothelial and muscle cells onto collagen-polyglycolic acid scaffolds. After 7 wks of culture in laboratory bioreactors, the autologous engineered bladders were used in a surgical reconstruction for patients with myelomeningocele. 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.

A few examples of regenerative medicine technologies already tested in patients are presented in Table 1. A wide array of engineered organs (urinary bladder, trachea, and cornea, or tissues (skin, cartilage, and muscle) are developed to the point of clinical applications. Many other regenerative technologies are under development in preclinical stages before 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 to regenerate damaged heart tissue in nonhuman primates. Investigators injected one billion heart muscle cells derived from human embryonic stem cells into the infarcted muscle of pigtail macaques. The group found that, during the 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 3 mos, the cells appeared to have fully integrated into the macaque heart. Future efforts by this group will work to reduce the risk for complications including arrhythmias.

Supported by preclinical 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 platforms. 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 trials.

### 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 protocols. 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 available products or services. 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.

#### TABLE 1: Regenerative medicine technologies applied to patient

<table>
<thead>
<tr>
<th>Engineered Organ or Tissue</th>
<th>Types of Cells Used</th>
<th>Scaffold</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Epithelial or none</td>
<td>Complex, multiple in use</td>
<td>Gunter et al. 24, 2012</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Urothelial, muscle</td>
<td>Collagen, collagen/polyglycolic acid</td>
<td>Atala et al. 10, 2006</td>
</tr>
<tr>
<td>Trachea</td>
<td>Epithelial, chondrocytes</td>
<td>Cadaver trachea</td>
<td>Wise 17, 2013; Berg et al. 16, 2014</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Mesenchymal stem cells, others</td>
<td>None</td>
<td>Pastides et al. 27, 2013</td>
</tr>
<tr>
<td>Cornea</td>
<td>Limbal stem cells</td>
<td>Amniotic membrane</td>
<td>Kruse and Cursiefen 19, 2008</td>
</tr>
<tr>
<td>Muscle</td>
<td>None</td>
<td>Porcine intestine submucosa</td>
<td>Mase et al. 32, 2010</td>
</tr>
<tr>
<td>Heart</td>
<td>Neonatal cardiac cells</td>
<td>Decellularized whole rat heart</td>
<td>Ott et al. 38, 2008</td>
</tr>
</tbody>
</table>
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. In this supplement to the American Journal of Physical Medicine and Rehabilitation, leading faculty at rehabilitation medicine programs across the country highlights examples of regenerative technologies under development or in current practice in rehabilitation disciplines.

**BETWEEN THE COVERS**

Gentile et al. provide an example of how rehabilitation modalities fit into a regenerative approach in a patient with limb trauma who received muscle cell transplantation onto a bioengineered scaffold. In this case study, a rehabilitation program was directed to optimize posttransplantation 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 describe the use of promising biologic and small molecule interventions in development for skeletal muscle regeneration. The authors discuss how new pharmacologic agents, such as selective androgen receptor modulators and myostatin inhibitors, might offset age- and disease-associated muscle wasting. Bruan et al. discuss how gene replacement therapy using adeno-associated virus offers new hope for patients experiencing neurogenerative muscle disorders, such as Duchenne muscular dystrophy and a rare inherited muscle disease, X-linked myotubular myopathy. Pourcho et al. 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 disk (Gou at al.) or to regenerate cells of the nervous system (Maldonado-Soto et al.) 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. Stem cells are also under study as biologic reagents to model inherited diseases using genetic reprogramming (Mack et al.). Finally, Behfar et al. 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 herein proposed:

“Regenerative rehabilitation integrates regenerative technologies with rehabilitation clinical practices to restitute 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 Web site: “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.” 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 physiologic 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 Medicine led by Dr. Joel Stein administrates 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 Web site, 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 United States 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 collaborates 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 where faculty in the Department of Rehabilitation Medicine finds their primary bench laboratory space. Both gene therapy and stem cell projects are underway by rehabilitation scientists working in the laboratory space at the Institute for Stem Cell and Regenerative Medicine.

**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 is essential. Working groups and consortium with the participation of scientists, rehabilitation physicians, and physical therapists involved in the areas of regeneration and rehabilitation are of critical importance. In this regard, the University of Pittsburgh together with other rehabilitation centers in the United States 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 an 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 provides guidance for future decision making about structuring regenerative rehabilitation activities:

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**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.

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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 approximately 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, grant 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 constitutes an emerging field focused on the repair and functional restoration of organs damaged from diseases, trauma, and degenerative conditions and is built to represent the future of medical care. Understanding the principles of regenerative medicine is essential, and incorporating them into rehabilitation medicine is critical to drive validated science into clinical options that will allow us to build a model of care that has the potential to change a letter in the word CARE to transform it into CURE. In this supplement, the readers will find many examples of translation of regenerative rehabilitation principles into clinical practice. The authors expect that this supplement represents one of the multiple initiatives to contribute to the further development of the field of regenerative rehabilitation medicine.

REFERENCES

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