

Biologics and Regenerative Medicine- What's New, What's Next

It is an exciting time in regenerative medicine. We are witness to an unprecedented explosion of knowledge and innovation in both basic and translational science, as well as clinical application. The great possibility of the application of biologically driven therapies holds great interest and hope from patients, practitioners, academia, and industry alike. The opportunity to cure un-curable or difficult to treat disorders and diseases captures and holds the interest of patients who are one of the key drivers for innovation. Patients are becoming keenly aware of the science and treatment options. Along with rapid availability of new therapeutics and possibly the application of unapproved treatments, worldwide regulatory bodies are under pressure to ensure treatments are safe and efficacious. The first response has been uniformly suppressive by key international regulatory bodies; followed by comprehensive legislative enactment. Currently, there is a prime opportunity for the medical community to follow recent legislative enactments and provide a comprehensive framework for self-governance. Additionally, there is an unprecedented opportunity for stakeholder collaboration and community building. The result could be a system where all who seek care have access, where medicine provides solutions and science of medicine advances unfettered, industry grows, and regulating bodies are harmonious. The future is quite bright in regenerative medicine with technology such as personalized biological products, needle-less injections, tissue targeting, gene editing, and immunotherapies as solution(s) on the horizon to address the current gap(s) in treatment.

Regenerative medicine holds such great promise and excitement that many of us believe we are standing witness to a fundamental shift in the practice of medicine that could favorably alter the course of humanity. Regenerative medicine is defined as the treatment of medical conditions that harnesses the human body's inherent ability to regenerate tissue at the level of cellular or organ structure, that foster cellular communication, translation, organ system refurbishment, and result in overall organism well-being. Strategies of treatment include healing response, exogenous augmentation, cellular signaling, external stimulus, and genetic influence/modification. It is here that lies the great excitement, that human beings become the source of their well-being and health. The concept is very inspiring. Specific to musculoskeletal disease we have a growing body of evidence that is supportive of innovative approaches/preparations such as platelet rich plasma for the treatment of knee osteoarthritis¹⁻³, to augment rotator cuff repair^{4,5}, and promising data in the area of treating tennis elbow, partial ACL (anterior cruciate ligament) tears, and plantar fasciitis with platelet based products; bone marrow derived products offer promising data for augmenting rotator cuff repair^{6,7}, treating shoulder and knee osteoarthritis^{8,9}, and ACL tears¹⁰; adipose derived products also have promising data for treating knee osteoarthritis¹¹; and developing evidence exists for peripheral blood products for augmentation of surgically treated focal and diffuse cartilage defects in the knee with ongoing Phase IIb clinical trial in the United States¹².

Although it may not seem apparent, the underlying purpose of regenerative medicine may not be just for curing a disease, but for the perfection of human organism, and possibly physical immortality. Currently, unclear and restrictive regulatory barriers in the developed world are presenting challenges for all involved, and in many cases logical and accessible treatments become inaccessible. This is not new, though we have seen this in the past¹³. Recently, the United States approved the 21st Century Cures Act and accompanying Food and Drug Administration (FDA) draft guidance for Human and Cellular 5 Therapeutics/Products (HCT/P) provided another pathway for biologics that is an alternative to the standard phase pharmaceutical pathway and created a new category of biological product called regenerative medicine advanced therapy (RMAT). To date over 14 products have been approved¹⁴, however, it remains to be seen the actual impact on clinical practice. Although the rapid expansion of the field has outpaced regulation globally with few exceptions, existing rules have provided little guidance for both clinicians and scientists on the best way to proceed. The questions about, and definitions of, certain biologic products are currently under debate in the United Kingdom¹⁵, European Union¹⁶, India¹⁷, as well as Australia¹⁸. Despite the lack of national or international harmonization of regulation, it appears that regenerative medicine moves forward and relatively newly formed societies such as the American Academy and Board of Regenerative Medicine are engaging in active dialogue with FDA; there seems to be room to influence the course of action.

The regulatory, research, and clinical attention on regenerative medicine and its related products suggests they are here to stay. The market has grown quite significantly overall from 2012 through 2016 by nearly 100% according to the actualized by the stem cell therapy index (SCTI)¹⁹. With the acceptance of cellular therapies, comes a prime opportunity for practitioners in the space to collaborate and create self-imposed standards for regulation and harmony across practices. This can be done by peer-to-peer knowledge and best practice sharing; creating the required processes for defining the conditions that have the most evidence for treatment, determining the best candidates for treatment, candidate assessment and selection, and informed consent. Additionally, creating standard operating procedures (SOPs) for sample collection and handling, cellular processing, 6 treatment administration, outcome and adverse event management and reporting are opportunities in the industry. Guidelines are currently

being debated and established by regulators in the precarious position of balancing the protection of patients with clinical progress and scientific innovation. Practitioners can assuage the concerns of the regulators by self-imposition of more rigorous clinical practices, with self-policing to limit bad actors and encourage good and ethical behavior.

The growth of investigations in the regenerative medicine space has grown upwards of 300% since 1996¹⁷. The overall community has witnessed unprecedented levels of collaboration at both the academic and community levels. This has come in the form of multi-centric trials and the creation of network, community based clinical registries. With this, remains great opportunities for the strong growth of evidence-based research and peer-to-peer learning coupled with joint advocacy activity. The strength in numbers and shared common interest allows for the opportunity for powerful advocates. Additionally, as consensus among stakeholders is established, the collective strength available will effectively shape the regulatory conversation and subsequent policy.

The future is present, and innovations abound. New technology is transforming the way that care is delivered to patients. Needle free injection technology (NFIT) is a broad concept that includes a wide range of drug and or cellular delivery systems that administer injectates through the skin by either shockwave, pressure via gas or electrophoresis that eliminate the need for hypodermic needle. These systems are able to administer highly viscous products which cannot be administered by traditional needle and syringe systems, further adding to the usefulness of the technology. Another innovation is the use of nanogold particles to induce increased production of regenerative cytokines and growth factors to treat degenerative spine, joint, and tendon disorders²⁰. Despite being a relatively new technique, chimeric antigen receptor T cell (CAR-T) immunotherapy has gained significant ground for treating both blood based and solid tumor malignancies in recent years with approved therapies currently available for patients. What is little known is that this type of therapy is being used with traditional chemotherapeutics in the lower income countries to improve clinical outcomes at lower cost²¹. Additionally, it is also at the investigational stage for other auto-immune disorders that affect bone and joints. Capabilities to identify genetic abnormalities that affect bone and joint conditions have really been critical in advancing therapeutics directed specifically at underlying abnormalities. With the advent of iPS (induced pluripotent stem cells) and CRISPR (clustered regularly interspaced short palindromic repeats) the possibility of editing genes has become a reality. SMART cells (Stem cells Modified for Autonomous regenerative therapy) are one such engineered product that can secrete proteins that antagonize catabolic cytokines such as IL-1 and TNF- α that is rapidly responsive and self-regulated²².

The future is bright, and exciting. Full of possibilities and creations not even conceived yet, coupled with unfettered collaboration, the multiverse is the limit.

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Pam Jackson PhD
Infohealth, FZE, Dubai, UAE

William D Murrell MD
Emirates Integra Medical and Surgery Center
Dubai Healthcare City, Dubai, UAE
Emirates Healthcare, Dubai, UAE