Orthobiologics: Early Adopters are Innovating the Regenerative Medicine Industry with Clinical Results

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Biologic and cellular therapies have made a major impact in orthopedic surgery over the past several years. These treatments, which range from using a patient's own tissues and cellular materials to artificially produced proteins, are increasingly well characterized in the scientific literature and are being rapidly integrated into daily orthopedic practice. Traditionally orthopedics has been an early adopter of regenerative medicine concepts and therefore has emerged as an important sector in testing and shaping the future for cellular therapies and regenerative medicine.

This review will provide an overview of biologic and cellular therapies as they pertain to orthopedics. Specifically, the use of biologics and cellular therapies in orthopedics, the market for such therapies, and existing and emerging technologies will be explored. Lastly, this article looks to the future of regenerative medicine for orthopedic applications and how developments occurring today on a spectrum of fronts may impact the overall future of biologic and cellular therapies.

Biologic and Cellular Therapies in Orthopedics

The field of orthopedics is primarily concerned with the treatment and correction of diseases and injuries of the musculoskeletal system. Within orthopedics there are several sub-specialties. These include, in broad stroke, joint arthroplasty, sports medicine, back surgery and trauma care. Orthopedists' primary goal, across sub-specialties, is helping patients with musculoskeletal problems return to normal life activities as rapidly as possible. Orthop edists accomplish this goal using a variety of tools from metallic implants (i.e., artificial knee) to pharmaceuticals and physical therapy. Orthopedists also have a tradition of utilizing biologic materials, such as tendon grafts and deminerlized bone, to accomplish their surgical goals. This tradition has provided a foundation from which orthopedists have begun to utilize biologic and cellular therapies to help patients and to improve the function of traditional tools. The successful integration of products such as Medtronic's Infuse® bone morphogenic protein, which induces bone growth, into surgical care highlights orthopedist continued interest in and desire for biologic and cellular therapies can improve patient care.

Across sub-specialties, orthopedists are increasingly looking to biologics and cellular therapies to improve patient care. There are two primary reasons for this: 1) to improve the efficacy of implants and surgical procedures; and 2) to reduce, or eliminate, the need for invasive surgery.

Orthopedic implants have a long and well documented history. For decades, patients have reaped the benefits of new and improved implants, graft materials, and improved techniques. These improvements have made standard orthopedic procedures, ranging from joint replacement and broken bone fixation to tendon repair, relatively low risk and highly effective. Despite this success, room remains for continued improvement.

Areas ripe for continued improvement include the bone-implant interaction, graft integration and sourcing, and infection control, all of which, if improved, could lead to more rapid healing and faster recovery. Currently, investigations are on-going in all of these areas utilizing a variety of biologic and cellular therapies ranging from the use of a patient's own fluids and tissues to promote accelerated healing to the use recombinant proteins to promote bone growth and attachment to metallic implants.

Concurrent with investigations targeted at improving the effectiveness of implant and surgical techniques, orthopedists are exploring ways biologic and cellular therapies can be used to eliminate the need for invasive surgeries and the use of certain, potentially harmful, pharmaceuticals. Clinic based, non-invasive, therapies that allow a surgeon to implant cells into native tissue to regenerate or improve its functionality are under study and showing promise. Similarly, human studies utilizing a patient's own cells to treat tendon disorders, such as tendonitis, are underway and appear to be a potent alternative to steroid injections for pain control.

Orthobiologics

The market for biologic and cellular therapies in orthopedics is commonly referred to as the Orthobiologics and is made up of a select group of products that range from recombinant growth factors

to synthetic matrices and bone void fillers. In 2007. the market for Orthobiologics was estimated to be worth approximately US$4.2 billion with an annual growth rate of 17%, making it the fasted growing segment in orthopedics. Within the overall orthobiologics market, growth factor and stem cell therapies are forecasted to be the fastest growing categories, with the combined market reaching US$3.6 billion by 2012.[1] Overall, it is projected that the robust orthobiologics market will almost double by 2012 as average population age increases and technology advances.

Growth Factor Therapies

Growth factor therapies are currently made up of two main product types. The first of these are recombinant growth factors, such as transforming growth factor-beta (TGF-beta), platelet derived growth factor (PDGF), fibroblast growth factor (FGF), and bone morphogenic protein (BMPs are commercially available as Infuse® produced by Medtronic and OP-1 produced by Stryker Biotech). First isolated in 1965 by Marshall Urist,[2] and commercialized beginning in the late 1990s, BMPs and other follow-on proteins currently under study have become useful tools orthopedists can use to manipulate cellular behavior in and around an injury or reconstruction site. To date, these powerful, commercially produced proteins have been the primary market drivers and have the advantage of being mass-produced and readily packaged, similar to pharmaceutical products. There are, however, serveral disadvantages. Among the most important disadvantage widely addressed in the scientific literature is the unknown biologic cascade effects that these highly concentrated proteins may have (safety). In addition, costs associated with the development and discovery of new, efficacious proteins (pipeline/opportunity costs) as well as the straight product procurement and use cost for these products (US $5000.00 per use) raises some concern.

While these products clearly have a place in the future of orthobiologics, recent reports on the widespread off-label use and promotion of these products, combined with post- surgical complications (primarily hypertrophic bone growth) and the continued pressure to curb per procedure costs, make the future of recombinant growth factor products less clear than was originally thought a year ago. It is likely this uncertainty will continue, or potentially accelerate, as follow up studies continue and new, potentially less risky and more economical technologies emerge.

The second category of growth factors are the platelet-derived growth factors. Platelet-derived growth factors are commonly obtained by collecting a sample of a patient's own blood, processing this blood via centrifugation or other separation means to concentrate the platelets, then applying the platelet-rich plasma (PRP) concentrate to an injury site. The basic biology of PRP is well documented in the research thesis by Dr. Peter Everts, published in 2007, titled "Autologous Platelet Leukocyte Enriched Cell Bone Efficiency". In brief, platelets contain a cascade of growth factors within their cell walls. Example growth factors found in platelets include platelet-derived growth factor (PDGF), transforming growth factor beta (TFG-beta), insulin like growth factor (IGF), and vascular endothelial growth factor (VEGF), among others.

Once platelets are lysed, a cascade of autologous growth factors are released at the application site inciting angiogenesis (blood vessel growth) to jump start the healing process. The advantages of platelet-derived growth factors are several. Primary among these is the ability of platelet-derived growth factors to act on multiple levels within the healing cascade. Unlike the recombinant growth factors that dose a site with a single concentrated protein that has one action along the healing cascade, platelets release a cocktail of growth factors that act both individually and in concert with other cells and proteins to provide an increased healing response. Additional advantages to platelet-derived growth factors include their relatively low cost, inherent safety (autologous) and their ability to act on multiple tissue types to speed healing. Disadvantages of platelet-derived growth factors in orthopaedic use include their inability to directly stimulate bone formation, something recombinant growth factors in the BMP have demonstrated. There are also inherent difficulties in processing and handling bodily fluids at the point of care (bedside).

Despite these concerns, the benefits associated to platelet-derived growth factors have gained widespread adoption in orthopedics. Recently, there has been an explosion of scientific investigation into platelet-derived growth factors and their efficacy in treating multiple orthopaedic problems.[3] As the scientific literature mounts, surgeons and patients become more familiar with platelet-derived growth factors, and cost containment continues, it is likely the adoption rate for platelet-derived growth factors will accelerate. This is especially likely as the technologies used to process, handle, and deliver platelet-derived growth factors advances.

Stem Cell Therapies

The development of stem cell therapies to treat orthopedic disorders is advancing at a rapid rate. The promise of being able to regenerate multiple tissue types critical to proper musculoskeletal function has lead industry forecasters to predict the market for orthopaedic focused stem cell therapies growing from its current size of US$110 million to US$950 million by 2012[4] representing a CAGR of 53.9%.

Development of orthopedic focused stem cell therapies has been focused on creating products that can regenerate tissues such a cartilage, replace traditional autografting techniques, such as harvesting bone from the iliac crest for use in reconstructive procedures, and infusing matrices with cellular material to speed integration. Currently, there are a handful of stem cell therapy products, such as DePuy's Cellect Cell Capture Technology, Harvest Technologies BMAC System, BioMet's Marrowstim and NuVasivis' Osteocel on the market that have been rapidly adopted by the orthop edic community. Many more are in development and early phase clinical testing.

The primary cell utilized in orthop edic stem cell therapies is the bone marrow derived mesenchymal stem cell (MSCs).[5] These adult stem cells are found in bone marrow and have the ability to differentiate into multiple types of tissues ranging from cartilage and bone to tendon and muscle. Studies have demonstrated that bone marrow derived MSCs when applied in sufficient quantity have therapeutic ability and can regenerate tissue.[6] Currently, the bulk of evidence supporting MCSs ability to regenerate tissues and provide therapeutic benefit comes from the cardiovascular arena, but

orthopedic investigations are rapidly documenting similar results. Additional cell types under investigation include fat-derived (adipose) stem cells, umbilical cord-blood derived stem cells and amniotic fluid-derived stem cell.[7] While these non-bone marrow derived stem cell sources appear promising, for orthop edic application it appears that adult bone marrow derived stem cells will be the primary source of MCS for orthopedic application.

Until recently, orthopedic focused stem cell therapies generally utilized the model of procuring bone marrow from adult donors, processing the bone marrow in a lab, and growing large quantities of bone marrow derived stem cells that could be packaged and distributed similar to a pharmaceutical product. Nuvasive's Osteocell is one product that has taken this approach.

An alternative to this approach is utilizing is procuring and processing a patient's own bone marrow at the patient's point of care. Investigations have demonstrated that in addition to the inherent safety associated with utilizing a patient's own bio-materials, additional benefits, such as increased cell activation and proliferation, are derived from combining autologous stem cell therapies with autologous blood derived growth factors (i.e., PRP). As technologies for the procurement and processing of a patient's own bone marrow at the point of care advance, it is likely these systems will be rapidly integrated into standard orthopedic care models.

Improving the Standard of Care

The use of growth factor and stem cell therapies in orthopedics, while growing, is still in its infancy. Questions regarding efficacy, appropriate indications for use, and optimized delivery systems remain and require continued investigation and development. Despite these questions, it is clear that orthobiologics is a growth area with the potential to greatly improve orthopaedic care. Groups and companies advancing the state of the art in regenerative medicine are emerging on a world-wide basis. Over the next several years as the Orthobiologics market place matures it will be increasingly important that these entities work with appropriate stake holders, such as regulators, medical thought leaders, and educators, to ensure safe and effective products are brought to market.

Addressing Point of Care Cell Procurement: Circle Biologics, LLC

In order to address the needs of point of care cell procurement, Circle Biologics, LLC has developed a system of devices intended to advance the point-of-care applications of regenerative medicine. Circle has focused product design to meet the versatile needs of multiple cellular therapy sourcing and processing requirements. With a single device platform (See Figure 1), the company is striving to bring broad market utilization by standardizing the process across several therapies (i.e., PRP, stem cell, and tissue enrichment/generation). Additionally, Circle has developed solutions that address the entire procedure—from procurement to processing to delivery or implantation—with a streamlined combination of devices that spare cells, reduce outside exposure, and protect the user and recipient. Through its versatile, common-use platform, Circle is working to bridge the gap between *in vitro* findings and clinical results thus providing a seamless translation of discovery and development to product.

Conclusion

Regenerative medical technologies are advancing the standard of care in orthopedics. Orthopedics is unique among surgical specialties in terms of the tangible clinical benefits regenerative medical technologies will deliver to improve patient quality of life; measuring the extent and time to healing of bone is relatively easy to quantify. Stake holders in the field of orthopedics continue to be interested and open to advancements in the regenerative medicine arena. This broad based interest points to a future where the physicians who treat individuals suffering from orthopedic aliments will have additional options for ancillary, and perhaps definitive, biologic and cellular treatments that accelerate healing and improve their quality of life.

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Matthew R Kyle is President and CEO of Circle Biologics, LLC, an emerging medical device company focused on cellular and biomaterial management systems. He has more than 10 years of entrepreneurial experience combining technical, legal and business knowledge to build and guide small cap medical companies. Prior to becoming President of Circle, Mr. Kyle directed operations and acted as general counsel for Millennium Medical Technologies, Inc., an orthopaedic trauma device focused development entity. At Millennium, Mr. Kyle managed the development and sale / transfer of seven (7) organically developed medical devices to consolidating entities. While at Millennium, Mr. Kyle implemented robust quality system that improved R&D efficiency, product time to market and overall product value. Mr. Kyle has lead and developed robust intellectual property and regulatory programs resulting in multiple issued patents and regulatory approvals in both the US and overseas.

Mr. Kyle is focused on managing multi-disciplinary teams in milestone critical environments, emphasizing value creation and ethical medical device development. He is a named inventor on one issued patent and is a named inventor on several additional pending patents.

Mr. Kyle holds a Juris Doctor degree from William Mitchell College of Law, St. Paul, MN and bachelor degrees in Economics and Biology from St. John's University, Collegeville, MN. He also participated in Stanford University's Bio Design Program, where he was selected to participate in the "Emerging Entrepreneur's in Biomedical Technology" program.

Kyle Swartout

Kyle Swartout is the Vice President of Sales and Marketing with Circle Biologics. Mr. Swartout brings strategic market development abilities from diverse positions held with large biotech companies, including Pfizer, Zimmer, and Smith & Nephew. He has worked with several start-up companies in the medical device and service sectors with special emphasis on market identification, sales strategy, global sales force recruitment, corporate partnerships, product logistics, product design, product portfolio expansion, licensing, product divestment, and fundraising. His extensive clinical experience lends to a customer-focused approach to product design and marketing initiatives. Mr. Swartout holds a bachelors degree in Biology, with high honors, from Carleton College (MN).

Richard F. Kyle, M.D.

A graduate of Loyola University Chicago Stritch School of Medicine in Maywood, Ill., Dr. Kyle is currently chairman of the department of orthopaedic surgery at the Hennepin County Medical Center in Minneapolis. He is also professor of orthopaedic surgery at the University of Minnesota and medical director of the university's biomechanics laboratory, specializing in trauma and adult reconstruction orthopaedics.

Dr. Kyle is active in numerous professional organizations and serves on the board of directors for the Minneapolis Medical Research Foundation, the Midwest Orthopaedic Research Foundation and the Twin Cities Orthopaedic Education Association. He is a founding member and past president of the Orthopaedic Trauma Association and a member of the American Orthopaedic Association, the American Association of Hip and Knee Surgeons and the Orthopaedic Research Society. He has served on many AAOS task forces and committees.

Dr. Kyle has published two books and has authored 17 book chapters and 60 scientific journal articles. He has given more than 300 presentations—both nationally and internationally—on a variety of topics, including fractures of the long bones and major joints, as well as total shoulder, hip and knee replacement

The recipient of numerous honors and awards, Dr. Kyle has served as a visiting professor at the University of Hong Kong, at the Virginia Commonwealth University (Richmond, Va.), at the Utah School of Medicine (Salt Lake City) and at the University of Colorado Health Sciences Center (Denver). He is an honorary member of the New Zealand Orthopaedic Society and the Argentine Association of Orthopaedics and Traumatology, and has been named a "Top Doctor" by Mpls.St.Paul Magazine for seven consecutive years.

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