NEXT-GENERATION ORTHOPEDICS: BIOLOGICS

Unlocking living architecture potential and engineering fitness

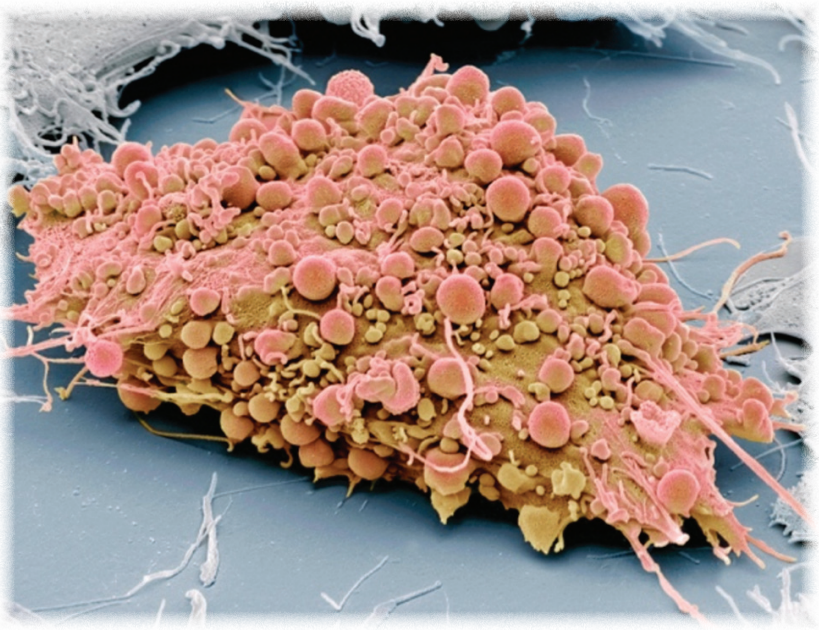
Digital health innovations have made it possible for us to use portable devices to access medical information, monitor vital signs, take tests at home and carry out a wide range of tasks. A recent article in the *New England Journal of Medicine* cited physician concern that these innovations can come at the expense of the human connection at the core of the patient physician relationship of trust, given the vanishing need of a stethoscope. The diagnostic utility of the stethoscope is obvious, but some will ask, will the loss of the symbolic and ritual connection change the perception of trust?

by Carri Allen Jones, MD

In a parallel fashion, could orthopedic procedures such as arthroplasty become obsolete, or the arthroscope, a historic instrument found in the Smithsonian?

Many in sports medicine agree the advancement in arthroscopy over the last few decades has been one of the greatest innovations in orthopedics. More recently stem cell applications, tissue engineering, and 3-D bioprinting have emerged as the next generation of orthopedics.

The potential benefit of orthobiologics and stem cells in sports medicine gained public interest in 2009 with the news story on Pittsburgh Steeler player Hines Ward's ability to return and play in the Super Bowl after sustaining a MCL tear two weeks prior. His treatment with PRP (platelet rich plasma) heralded an expedited recovery. Subsequently, a parallel rise in public and practitioner interest and usage occurred.



Stem cell therapy is gaining momentum as a clinical option in orthopedics. However, high level research on the technology's efficacy has not been completed and long-term safety unknown. The general scarcity of information from large randomized controlled trials emphasizes the need for rigor when considering stem cells for treatment in orthopedic conditions. Bioethics and regulatory concerns remain, as clinical usage of stem cell therapy is outpacing the evidence. The Center for Biologic Evaluation and Research, a division of the FDA, released preliminary guidelines for regulation in 2014. Most likely a heightened wave of regulation will occur within the next few years, yielding a capitulation of clinic closures due to non-compliance, poor quality assurance, and unsubstantiated claims. The corollary, improved concentrated rigor in orthopedic regenerative medicine should emerge to further advance tissue engineering, 3-D bioprinting, and gene therapy.

Basic science of treatment

Stem cells may be derived from allogeneic and autologous sources. Allogeneic mesenchymal cells (MSCs), for example, can be derived from the placenta, umbilical cord, or umbilical cord blood. Autologous stem cells include endothelial progenitor cells sourced from bone marrow or peripheral blood, hematopoietic stem cells, adipose-derived stem cells, and the most commonly used type, MSCs, derived from bone marrow. Both the ideal type and number of stem cells needed to treat specific clinical conditions is unknown.

Bone marrow-derived MSCs are the most reported stem cell type used in the literature. It is estimated more than 100,000 U.S. adults receive cellular therapy each year in which clinicians use a point of care same-day procedure to harvest bone marrow aspirate, concentrate the aspirate by centrifugation, followed by injection of the cells into the treatment area.

The number of stem cells harvested varies depending on the practitioner isolation technique, donor age, donor health status, and medical device used for processing. Also, the cell count number is limited to the retrieval harvesting passages and cannot be expanded in cell culture in the United States.

The ability of stem cells to replicate over long periods, and their extended life span, are the features that generate the most enthusiasm. Once delivered, these multipotent cells can differentiate into bone, cartilage, tendon, ligament, and endothelium. They also release a number of bioactive factors stimulating tissue repair and wound healing, along with other paracrine signaling behavior for daughter cells and possible homing. Cellular analysis and characterization of the graft material confirm the pluripotent nature, allow cell sorting and surface marker identification, genomic sequencing, along with the number of nucleated cells prior to implantation.

Platelet-rich plasma (PRP) is plasma enriched with a 3-5 fold higher concentration of platelets than baseline whole blood. PRP is considered an orthobiologic and has gained support in orthopedics for its utility in restoring function more quickly, hastening recovery. Platelets and white blood cells are a rich source of bioactive growth factors that can modulate the healing process. When activated they release growth factors that act locally to recruit undifferentiated progenitor cells to the site of activation, trigger mitosis, and initiate tissue regeneration and remodeling. Further classification of PRP has been recommended to influence greater inter- and intra-operative clinic reliability for uniformity of reporting and tracking data. This includes PRP with or without leukocytes, and PRP with or without activation. Also, one step further that may be considered is the number and type of white blood cells given different characteristics of granulocytes, lymphocytes, and monocytes.

Growth factor concentration in any PRP preparation is directly proportional to the amount of platelets captured. The greater the growth factor amount, the greater the response and recovery of the target tissue. Many do not realize all PRP is not equal. The amount of platelets collected may vary with speed of venipuncture, processing equipment, centrifugation time, radius distance from center of the centrifuge, soft versus hard spin, anticoagulant, and use or no use of an agonist activator.

The mechanism of some of the key growth factors involved in the healing process include upregulating other growth factors as a chemo attractive for stem cells (Platelet Derived Growth Factor, PDGF), stimulating angiogenesis and neovascularization (Vascular Endothelial Growth Factor, VEGF), stimulating migration and adhesion of progenitor cells (Stromal Derived Growth Factor), and promoting cell mitosis and differentiation for connective tissue and bone (Transforming Growth Factor Beta, TGF-B). One of the most important functions of platelets is their role in promoting angiogenesis, as the re-establishment of blood flow through angiogenesis is critical for healing.

Recent studies indicate the optimal platelet concentration to stimulate angiogenesis ranged from 1.5 million to 3.0 million platelets per microliter (Giusiti et al, *Transfusion*, 2009).

Stem cellular biologics injected precisely under live dynamic ultrasonography or fluoroscopy into the area of an incomplete tendon or ligament tear, meniscal tear, subchondral bone marrow lesion, osteoarthritic joint, or lumbar disc annular tear has revealed promising results with diminished pain, improved function, and in some cases, improved living architecture radiologically. The limitations of the studies are the lack of robustness, methodology, study power, and often confounding variables and potential bias.

Augmented reality: Osteoarthritis as a health rift

Pain is an enormous global public health problem. One of the leading causes of pain is the escalating prevalence of osteoarthritis that is associated with an extremely high economic burden. This burden is largely attributable to the effects of disability, comorbid disease, and the expense of treatment. The occurrence of OA is increasing due to an aging population and obesity. approximately one-third of direct osteoarthritis (OA) expenditures are for pain medications. Another half of the cost is for hospitalizations for arthroplasty.

Emerging technologies can be immersive to solve the burden of this disease. Can augmented reality illustrate the role of new technologies, touring the individual amongst treatment regimens while empowering their decision for engineered fitness and avoidance of pain and disability? Can the reality of the pathogenesis of osteoarthritis be altered through genetic engineering? Can behavioral modeling through gamification challenge extreme detrimental joint activity? Can we incorporate protective wearable alarms? Can we be a molecular anthropologist and unlock the heritable multi generational forces that shaped the individuals epigenomic information?

Function follows form

Biodesign and tissue engineering have lead to the potential of 3-D bioprinting in orthopedics. This innovative technology allows the creation of organized 3-D tissue constructs via a "layer by layer" deposition process. This process also allows the combination of cells and biomaterials in an ordered and predetermined way. Current research applications are focused on cartilage bioprinting and regeneration. The capability to re-grow living tissue at the core of the complexity remains a major challenge due to the differences in cell types, matrix components, and organization for hyaline cartilage regeneration.

A more recent promising approach is using mesenchymal stem cells or chondroblasts as the cellular matrix in the scaffold structure. Designing the formed scaffolding with the chondrocytes embedded would change their function and morphology based on the extracellular matrix. Influenced by design, with function following the form.

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Current challenges

Although research in stem cell applications in orthopedics and cartilage bioprinting is growing exponentially, there is lack of robust and rigorous in vivo studies that can validate the long term capability of cells and material to regenerate.

Osteoarthritis is becoming more recognized as a disease of the subarticular region and as a whole, an organ undergoing failure. Bench to bedside translation of cellular therapies is in its infancy. It represents great hope and a possible paradigm shift in the medical model of arthroplasty to the possibility of upstream measures where painful orthopedic conditions become rare and the socio-ecological forces of burden diminished. ▪

About the author

Carri Allen Jones, MD, is currently in practice at Remedy Medical Group in Redwood City, and Peninsula Orthopedic Associates in Daly City. She is also Chief Science Officer at X Tech Ventures. Dr. Jones is board certified in physical medicine & rehabilitation, pain medicine, and sports medicine, and fellowship trained in tem Cell Regenerative Medicine & Orthobiologics. She has special interest in design thinking for the intersection of technology, medicine, and the social sciences.