

## Current Status of Regenerative Medicine in Orthopaedics.

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**Abstract:** Regenerative medicine has shown great potential for treatment of various disabling orthopaedic disorders. Major research is on bone healing, where various osteoconductive molecules, stem cells, gene therapy have shown potentially beneficial role. Genetic disorders like osteogenesis imperfecta are also being explored for an effective cure through regenerative medicine. Regenerative medicine has also shown a promising future treatment modality for spinal cord injury. Various inflammatory disorders like osteoarthritis and rheumatoid arthritis can also be treated through regenerative medicine. A significant opportunity exists to improve the cancer therapy beyond the capabilities of traditional cancer treatments such as chemotherapy and radiation. Regenerative medicine is shaping these new therapies through the integration of its genomics, gene and cell therapy, small molecule drug discovery, and protein therapeutic capabilities.

The human body has a remarkable capacity to repair itself. Regenerative medicine seeks to support, stimulate, and enhance the body's natural repair mechanisms to help them heal defects that they could not normally heal on their own. Regenerative medical treatments aim to either encourage the regeneration of healthy tissue at the site of injury itself or begin to grow new tissue outside the body (in a bioreactor, for instance) for implantation into the defect site at a later date. Regenerative medicine has offered an unprecedented opportunity for developing new medical therapies for debilitating orthopaedic conditions and a new way to explore the fundamental orthopaedic biology. The impact of regenerative medicine in orthopedics can be summarized as follows:

**1) Bone healing-** Bone is a specialized connective tissue with a mineralized collagenous framework for skeletal support of the body. Bone is a unique tissue in that its ability to regenerate is more predictable than any other tissue in the body. However certain conditions like revision joint replacement, fracture nonunion, tumour reconstruction, spinal fusion present difficult situations where bone healing is a problem. Autogenous graft is considered gold standard but has got limited supply. Next available solution is allograft but they lack the osteogenic potential. Next came the synthetic bone graft substitutes which provide a scaffold for bone to grow but provide no osteoinductive properties to "induce" bone to grow. Regenerative medicine aims to explore the full potential of osteoprogenitor cells, osteoinductive matrix and osteogenic growth factors for bone healing and is currently based on uses of recombinant growth factors like bone morphogenic proteins, bone marrow, stem cells, gene therapy etc. InFUSE (BMP-2) was truly the first off-the-shelf osteobiologic that was osteoinductive, i.e. you can put it in a cell culture and bone will grow. This was clearly a revolutionary invention in the world of orthopedics and represented the first time that regenerative medicine hit the orthopedic market. Stem cells, when mixed with biomaterials known as scaffolds, can help regenerate bone growth. Approach involves either expansion of stem cells in monolayer and loading them into a porous scaffold prior to surgery or direct cell expansion within the scaffold, and implanting this novel construct back into the donor patient. *Krebsbach PH et al (1997)*<sup>1</sup> used bone marrow derived stem cells loaded on extra cellular matrices such as hydroxyapatite-tricalcium phosphate. After in vivo implantation into NOD/SCID mice bone formation was observed. *Schecroun N et al (2003)*<sup>2</sup> also reported formation of specifically mineralized bone-like nodules through stem cells under optimal environment. Gene therapy is based on the philosophy that by transferring genes into cells at a specific anatomic site, the osteoinductive properties of

growth factors can be used at physiologic doses for a sustained period of time for a more significant healing response. Demineralised bone matrix, coralline calcium phosphate, ceramics are commonly used carriers which enhance the delivery of genes or vectors at the anatomic site. Future research is focusing on development of novel products, such as micro patterned surfaces by bioengineering using nanotechnology for stem-cell growth.

**2) Genetic Disorders-** This is another potential area of work for regenerative medicine. Osteogenesis imperfecta<sup>3</sup> and osteoporosis are two common disorders which are being researched upon and can be considered the prototype of simple mendelian genetic disorders and multifactorial disorders respectively. Stem cells are very promising in osteogenesis imperfecta as they are capable of homing to the bone marrow and differentiation into osteoblasts. Rationale is that mutant osteoblasts as they turnover can be replaced with normal osteoblasts derived from transplanted stem cells. Stem cells not only provide osteoblasts, they also self renew, thus providing treatment for life. Transplanted stem cells also have a survival advantage over abnormal endogenous cells. Another promising strategy is Antisense gene therapy based on over expression of exogenously supplied normal gene. Various polymorphisms in vitamin D receptors, estrogen binding proteins, various growth factors like IL-6, osteocalcin can be linked with osteoporosis. Gene therapy approaches that result in expression of a therapeutic agent ( a transcription factor, growth or morphogenic factor) selectively to bone for stimulation of osteoblast proliferation and differentiation provide the potential to increase the skeletal mass in skeleton. Future research is focusing upon introduction of therapeutic genes into cells without altering their biologic properties, physiologic responsiveness, engraftment properties and differentiation program.

**3) Cartilage repair-** Repair of the cartilage poses a particular challenge for regenerative medicine. Because it is largely isolated from a blood supply, it does not have ready access to the repair cells that help skin, bone and other tissue types heal themselves more effectively; even small defects can therefore grow rapidly, leading to large-scale degeneration and instability around the site of injury. The use of stem cells to generate a suitable matrix for repair has gained recent popularity with the use of marrow stromal stem cells and perichondrial / periosteal progenitors most commonly employed<sup>4</sup>. They generate a hyaline matrix but little evidence of articular cartilage architecture. Current research is exploring the potential use of mesenchymal stem cells as a source for tissue engineering, as well as the combination of cells with biodegradable scaffolds. Various gene products eg. IGF-1, bcl-2, IL-4, BMP-2 & 7 are being studied

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to enhance the cartilage regenerative potential. Strategies are being developed to deliver appropriate bioactive factors that may optimize this regenerative process. These involve either direct delivery of the factors or delivery of the transgene coding for the factors. Cartilage tissue engineering is another promising approach of regenerative medicine to tackle this problem.

**4) Ligament and Tendon healing-** they have a high incidence of injuries and usually lead to instability and loss of function. With surgical intervention, the grafts (eg. In ACL reconstruction) are gradually replaced by scar tissue which is of mechanical inferior quality. In case of tendon injuries, problem of healing as well as complication of adhesion development is also there. Regenerative medicine aims to potentiate the healing of natural ligaments and tendons with a more biologic plausible tissue and to prevent the above complications. Meniscus engineering<sup>5</sup> is another field which is promising for treatment of meniscal injuries.

**5) Spine-** There are three main fields:

- o *Intervertebral disc degeneration-* It is characterized by progressive loss of matrix proteoglycans rendering disc more susceptible to injury and degeneration. Gene therapy has focused on up regulating the matrix synthesis utilizing BMPs, IGF-1, TGF- $\beta$  etc.
- o *Spinal fusion-* spinal fusion is a commonly performed yet often unsuccessful procedure. Strategies to enhance spinal fusion include use of extracted and partially purified proteins including BMPs, recombinant BMP-2 & 7 and gene therapy i.e. delivery of gene or osteoinductive factor itself.
- o *Spinal cord injury-* Ability of stem cells to incorporate into the spinal cord, differentiate, and to improve locomotor recovery hold promise for a cure. Stem cells have the ability to remyelinate the demyelinated injured neurons. SCs have neurotrophic, ECM, and cell adhesion properties that are favorable to axonal regeneration in the peripheral nervous system<sup>9, 10</sup>. Akiyama Y (2001)<sup>6</sup> reported functionally significant extensive remyelination of the cord after neural stem cells were transplanted into the demyelinated adult rat spinal cord. Iwanami A et al (2005)<sup>7</sup> showed that the bar grip power and the spontaneous motor activity of the stem cells transplanted animals were significantly higher than those of sham-operated control animals. Syková (2004)<sup>8</sup> reported varying degrees of improvement in spinal cord injury patients after autologous MSCs were intravenously delivered to nine people who had sustained spinal cord injury.

**6) Osteoarthritis<sup>4</sup>-** The treatment of osteoarthritis includes a wide spectrum of approaches. At present, with the exception of surgery, all other treatments are palliative. That is to say that many of these treatments relieve pain and increase function. However, on the basis of medical evidence, these treatments do not change the course of the disease. Surgical interventions, including joint replacement and osteotomy, reverse the progress of osteoarthritis and provide long-term improved function and pain relief for specific joints. The goal of treating osteoarthritis is to arrest and reverse its progress regionally or globally through biologic methodology. Meaningful progress for biologic intervention accumulates annually. Pluripotent mesenchymal cells can be coaxed into chondrocytes or stem cells. Cytokines, growth factors, chemokines, protease inhibitors, kinases, apoptosis,

mechanics, and genetics are increasingly recognized to play key roles in the control of the articular cartilage behavior. Modulating IL-1 is a promising strategy to retard the progression of osteoarthritis. Gene replacement, gene control and gene addition are new areas of research for gene therapy for osteoarthritis.

**7) Rheumatoid arthritis-** Haematopoietic stem cell transplantation (HSCT) is now being investigated as a potential therapy. It is especially useful in severe refractory rheumatoid arthritis unresponsive to conventional therapies<sup>12</sup>, including tumor necrosis factor-alpha blockade and is well tolerated in patients with rheumatoid arthritis. Level of disease activity and progression of joint destruction in rheumatoid arthritis closely parallels the IL-1 levels in plasma and joint fluid. IL-1 receptor antagonist (IL-1ra) is a potential therapeutic agent for use in treatment of rheumatoid arthritis which is the focus for gene therapy for rheumatoid arthritis.

**8) Orthopaedic oncology-** A significant opportunity exists to improve the cancer therapy beyond the capabilities of traditional cancer treatments such as chemotherapy and radiation. It focuses on the development of cancer vaccines and angiogenesis inhibitors. Regenerative medicine is shaping these new therapies through the integration of its genomics, gene and cell therapy, small molecule drug discovery, and protein therapeutic capabilities.

**9) Other potential areas-** Avascular necrosis, Cystic lesions of bone, revision arthroplasties, tumor reconstruction surgeries are being explored as potential areas of research for regenerative medicine. Although the prospect of growing entire new knees, hips and shoulders is still decades from becoming a clinical reality, regenerative medicine holds real potential to improve the quality of care currently available to patients suffering from various orthopaedic problems. Surgeons, scientists and engineers are using a variety of tools, including advanced materials, cells, and biomolecules and engineering design tools to develop and refine new treatments, making regenerative medicine a truly interdisciplinary area of research and development in orthopedics.

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