

Tissue Engineering and Stem Cell Therapy

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What is tissue engineering?

Tissue engineering is a newly emerging biomedical technology and methodology. It encompasses a multi-disciplinary approach geared toward the development of biological substitutes designed to restore and maintain normal function in diseased or injured tissues. Tissue engineering includes three components, such as cells, biological factors, and biomaterials - are increasingly being applied in regenerative medicine, fuelled by better scaffolds and increased understanding of individual biofactors and cell sources. There are four fundamental technologies in tissue engineering: 1) the scaffolding for cell proliferation and differentiation, 2) the isolation and culturing of cells, 3) the drug delivery system (DDS) of growth factor, and 4) the maintenance of space to induce tissue regeneration. The combination of these technologies is able to assist and accelerate the regeneration and repairing of defective and damaged portions or whole tissues. For successful regeneration therapy of tissues and organs, it is important and indispensable to develop the technology and methodology of tissue engineering with biomaterials for molecular design and creation of a local environment which enables stem cells to enhance the proliferation, inducing cell-based tissue regeneration. Often, the tissues involved require certain mechanical and structural properties for proper functioning. The term has also been applied to efforts to perform specific biochemical functions using cells within an artificially-created support system. Regenerative medicine is often used synonymously with tissue engineering, although those involved in regenerative medicine place more emphasis on the use of stem cells to produce tissues.

The idea of tissue engineering arises from the problem that cell-based therapies rely on an intact scaffold (stromal connective tissue) of the diseased or injured tissue. Tissue engineering of cell scaffolding and DDS technologies that provide cells with a local environment suitable to induce tissue regeneration, is important to realize regenerative medical therapy. In addition, the scaffold and DDS technologies contribute to develop the basic research of stem cell biology and medicine as well as obtain a large number of cells with a high quality for cell transplantation therapy. A technology to genetically engineer cells for their functional manipulation is also useful for cell research and therapy. Several examples

of tissue engineering applications with the cell scaffold and DDS of growth factors and genes are introduced to emphasize the significance of biomaterial technology in new therapeutic and research fields.

Drug delivery systems (DDS) are expected to realize cell-based tissue regeneration therapy which have customarily been developed as part of the technology and methodology used to enhance the *in vivo* efficacy of therapeutic drugs. However, the DDS concept can also be used for prophylactic and diagnostic drugs to enhance their respective medical efficacy.

Stem cell and stem cell based therapies

A stem cell is a cell that has the ability to divide (self replicate) for indefinite periods—often throughout the life of the organism. Under the right conditions, or given the right signals, stem cells can give rise (differentiate) to many different cell types that make up the organism. Those, stem cells have the potential to develop into mature cells that have characteristic shapes and specialized functions, such as heart cells, skin cells, or nerve cells.

In recent years, the potential of stem cell research for tissue engineering-based therapies and regenerative medicine clinical applications has become well established. Stem cell-based approaches for the first time offer real hope that we in the future will be able to offer patients with currently intractable brain disorders effective treatments. However, we need to know much more about mechanisms of cell proliferation, differentiation and survival, and of regeneration and functional recovery. Research on different sources of stem cells and on endogenous neuroregenerative responses should continue in parallel. It is important to emphasize that the biologic problems that have to be solved in order to develop safe and effective stem therapies are complex and should not be underestimated.

The effectiveness of stem cell-based therapies and most tissue engineering concepts has not been demonstrated sufficiently in controlled clinical trials in the patients to be regarded as evidence-based medicine. In the meantime, the medical mantra “do no harm” should prevail, and the application of stem cell-based therapies should be done critically and cautiously, and treatment outcomes (good and bad) should be recorded and reported. Stem cell and tissue engineering research has exciting comparative and specific perspectives that most likely will benefit the health of humans. Controlled, well-designed studies are needed to move this new research field forward.

The application of biomaterial technology

Biomaterial technology plays an important role in the creation of the cell environment, such as the biomaterial scaffolds and the drug delivery system of biosignalling molecules have been investigated to enhance the proliferation of cell potential for tissue regeneration, such as cell scaffold and growth factors. Growth factors are often required to promote tissue regeneration because they can induce angiogenesis, which promotes a sufficient supply of oxygen and nutrients to effectively maintain the biological functions of cells transplanted for organ substitution. Total joint replacement with a cell-based, *in vitro*, engineered joint that will completely integrate *in vivo* and provide the recipient with life-long function is an often cited tissue engineering goal, but so far it is far from reality, because multiple biological and technical barriers exist due to our incomplete understanding of the developmental biology of bone, cartilage, and soft tissues, as well as the difficulty of storing whole organs prior to transplantation without cell and tissue death occurring. However, improved repair, if not regeneration, of focal defects like traumatic cartilage injuries may result from tissue engineering in the near future.

Stem cell and regenerative medicine

Regenerative biology as it applies to regenerative medicine is an increasingly expanding area of research with hopes of providing therapeutic treatments for diseases and/or injuries that conventional medicines and even new biologic drug therapies cannot effectively treat. Regenerative medical therapy have been expected to compensate for the therapeutic disadvantages of reconstructive surgery and organ transplantation, as well as create a new therapeutic strategy. The basic principle of cell therapy is very simple: to restore tissue function that has been lost due to damage or disease by replacing dead cells with new healthy cells through transplantation. Injection-based stem cell therapy is attractive because of its minimal invasiveness, the relative ease of the procedure, the ability of incorporated scaffolds to conform to normal anatomic form, and the reduced cost, morbidity, and decreased recovery time when compared with that of transplantation by open surgeries. Given the complexity of tissue structure and function, this prospect may seem remote. However, if cell replacement will work in the tissue, it could provide radical new therapies for severe degenerative disorders like Parkinson's disease and stroke. Whether it will work or not will depend on, first, if the grafted cells can survive and form connec-

tions in the patient's tissue and, second, if the patient's damaged tissue can integrate and use the grafted cells. Therefore, theoretically, it is possible that the injected, culture-expanded, stem cells have different characteristics from those of most of the stem cells in the original sample, which may lead to their reduced repair potential compared with that of nonexpanded stem cell populations. Several strategies are currently being investigated, cell therapies derived from autologous primary cell isolates, cell therapies derived from established cell lines, cell therapies derived from a variety of stem cells, including bone marrow/mesenchymal stem cells, cord blood stem cells, embryonic stem cells, as well as cells tissues and organs from genetically modified animals.

More and more scientists are trying to look for an effective methods to deliver gene for gene therapy. So that the new term of biomaterial appears and it is emerging in the area of regenerative medicine, which were combined with stem cell biology will accelerate the application of stem cell in the clinical treatment of damaged tissues. Biomaterial scaffolds capable of localized gene delivery are being investigated for numerous regenerative medicine applications and as model systems for fundamental studies of tissue formation. Scaffolds can be injectable, noninjectable, simple, complex, biological, or synthetic in nature. The scaffold must also degrade at a rate that optimizes cellular growth and tissue regeneration. The ideal scaffold has sufficient strength to protect cells from compression and shearing forces, while still having injury site anchoring potential and porosity to allow nutrient and differentiation factors to diffuse through it. Poly(lactide-co-glycolide) (PLG) was employed as the biomaterial for delivery, which has been widely used for a number of tissue engineering applications. Great strides are being made worldwide in our ability to synthesize and assemble nanoscale building blocks to create advanced materials with novel properties and functionalities. The optimal time point for evaluation of a scaffold-based treatment is also critical, and the best determination of treatment success can probably be made only after the "scaffold-tissue transition phase" has passed, which depends on the scaffold, cells, and tissue in question. The technological advances in transgenesis, tissue engineering and rapid prototyping (RP) have led to the development of spatially complex tissues. In cartilage repair models, the compressive load exerted on the injected cells and scaffolds has proven to be a major challenge; an attractive option for cartilage and bone repair may be injectable scaffolds loaded with stem cells that, after injection, undergo a phase transition to gel form, but this approach requires better scaffold materials than those currently available.

To realize this medical therapy of cell-based tissue regeneration, or so-called regenerative medical therapy, it is indispensable to develop a biomedical technology or methodology of tissue engineering that enables cells to enhance their proliferation and differentiation, leading to induction of tissue regeneration. Nanostructured surfaces have also been shown to elicit more favorable and selective biomolecule and cellular responses than surfaces at coarser length scales. These nanoscale attributes are enabling a variety of nanostructures to form the bases for a new field - nanomedicine. A fundamental issue in much of nanomedicine, and especially tissue regeneration, is to understand and to eventually control nanostructure-biomolecule interactions.

There have some surface immobilization biofactors, such as collagen, gelatin and fibronectin were used as reaction factors to coat the surface experimently and enhance surface immobilization. The collagen sponges of cell scaffold and gelatin hydrogels incorporating various growth factors for controlled release enabled the regeneration induction of various tissues. Fibronectin is used as one of important factors in the serum-free and feeder-free stem cell culture system. It modestly increased binding and transduction of the microbiological articles, yet did not significantly impact the delivery. Delivery of molecular vectors from PLG scaffolds could provide an efficient and versatile gene delivery system for use with in vitro and in vivo models of tissue formation, and ultimately for therapeutic applications.

Presently, extensive research in the area of regenerative medicine is focused on the development of cells, tissues and organs for the purpose of restoring function through transplantation. There is a recognized and imperative need for bioartificial organs. For example, while a bladder is a relatively simple organ, the breakthrough highlights the incredible benefits that can be gained from the cross-disciplinary nature of tissue engineering and regenerative medicine (TERM) that encompasses stem cell research and stem cell bioprocessing. An ideal artificial organ should provide nutrient transport system, mechanical stable architecture and synergetic multi-cellular organization in one construct. In cases with widespread fibrosis and scar tissue, cell-based therapies may fail, due to the lack of a blood supply and/or the lack of a microenvironment of receptors and biological mediators to provide the "niche" for attracting and supporting cell differentiation, proliferation, and function. The successful translation will require contributions from fundamental research (from developmental biology to the 'omics' technologies and advances in immunology) and from existing industrial practice (biologics), especially on automation, quality assurance and regulation.

It is believed that by combining a 3D porous template-scaffold-with an adequate cell population, it will be possible to develop bone and cartilage tissue equivalents that when implanted *in vivo*, could lead to the total regeneration of the affected area.

Bone tissue engineering and its application

Bone tissue engineering is an area of tissue engineering. Bone Tissue Engineering is an emerging interdisciplinary field that seeks to address the needs by applying the principles of biology and engineering to the development of viable substitutes that restore and maintain the function of human bone tissues. This form of therapy differs from standard drug therapy or permanent implants in that the engineered bone becomes integrated within the patient, affording a potentially permanent and specific cure of the disease state.

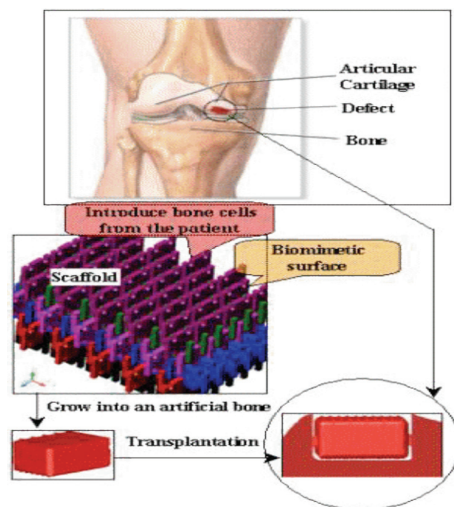


Figure 1: Bone tissue engineering using a scaffold as a template for tissue regeneration

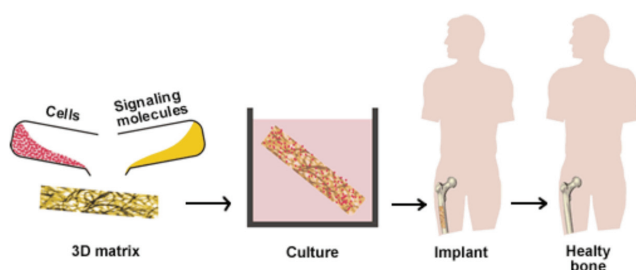


Figure 2. Scaffold-guided tissue regeneration.

you can't just harvest some cells, such as osteoblasts, then culture them to create a whole bone as depicted below in the bone tissue engineering:

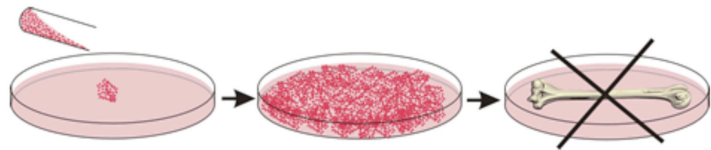


Figure 3. Simple culture techniques can't be used to grow organized tissue

In the tissue engineering, cell colonies need external cues or signals to grow into functional 3D tissues or organs. So the simple culture techniques can not be used to grow organized tissue.

The possible barriers in the bone tissue engineering include following areas. 1) how to insure angiogenesis in a timely fashion within the scaffold construct; cells without a blood supply will die, and mass infection will occur. 2) polymers have emerged as the principal material in bone tissue engineering. New biomaterials are needed that cause minimal foreign body response and that degrade in a completely predictable fashion. A synthetic bone scaffold must be biocompatible, biodegradable to allow native tissue integration, and mimic the multidimensional hierarchical structure of native bone. Various biomaterials including ceramics, metals, polymers, and composites have been investigated for their potential as bone scaffold materials. 3) A basic understanding of the spatial and temporal distributions of cells and growth factors required for osteogenesis, subject to particular disease states, must still be determined. 4) Readily available, safe, off-the-shelf supplies of osteogenic cells. 5) Advanced manufacturing systems are required that can fabricate complex scaffolds with spatially controlled distributions of materials, microstructures, cells and growth factors. 6) Design systems that encapsulate the tissue engineering knowledge-base and that understand the constraints of the manufacturing processes must be created to aid the next generation 'tissue engineer' in designing and manufacturing their products. 7) Critical-sized defects in bone, whether induced by primary tumor resection, trauma, or selective surgery have in many cases presented insurmountable challenges to the current gold standard treatment for bone repair.

Safety considerations of stem cell-based therapies

Safety of stem cell based therapy

The safety, both short-term and, in particular, long-term, of stem cell technologies is largely unknown. To date,

there have not been any reports of significant adverse reactions. However, this could be due to reporting bias. Use of the cells and technologies presented here in the regenerative medicine is likely to continue and expand in the near future. The establishment of a safety or adverse effect body, where unexpected clinical outcomes, is encouraged at this time. Until clinical efficacy has been proven, such an institution would, at least, be able to assess whether these procedures “do no harm.”

Safety concerns to consider include, but are not restricted to, aberrant cell development and tissue or vehicle contamination with infectious agents or foreign biological and nonbiological substances used in the laboratory processing of the stem cells.

Secondary to disease should be considered before instituting allogenic-based therapies. Overwhelming cell death of the injected cells could potentially impair tissue repair or, in more severe cases, trigger a significant inflammatory response. Safety considerations of stem cell-based therapies.

The aims to highlight clinical applications for the four areas of research listed above and will address a few key advances and a few of the hurdles yet to be overcome as

the technology and science improve the likelihood that Regenerative Medicine will become clinically routine.

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