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Where is dentistry in regenerative medicine?

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ABSTRACT

Where does dentistry fit into the field of regenerative medicine? Based on the fact that the goal of regenerative medicine is to restore function to damaged organs and tissues, it is apparent that dentistry, which has long embraced the concept of restoring function of damaged teeth, has embraced this goal from the very beginning. In this brief review we present the opinion that if you take as the primary criterion the restoration of tissue and organ function, dentistry has not only been at the forefront of restorative medicine but actually predates it in practice. We illustrate the depth and breadth of dental regenerative medicine using examples of therapies or potential therapies from our laboratories. These begin with an example from a historical area of strength, dental implant design and fabrication, progress to a more high tech bone scaffold fabrication project, and finish with a stem cell-based soft tissue engineering project. In the final analysis we believe that the restorative nature of dentistry will keep it at the forefront of regenerative medicine.

Key words: *Regenerative dentistry, regenerative medicine, implants, restorations*

The term regenerative medicine is thought to have been coined by Leland Kaiser, in 1992, in a hospital administration journal[1] where he posited that a new branch of medicine would develop that would attempt to change the course of chronic disease, and in many instances would be able to regenerate tired or failing organs. The tissue engineering concept had emerged earlier, as defined by Y.C. Fung in 1985[2] as an extension of the concept of biocompatibility. As the demands of medical devices became more complex, the definition of biocompatibility changed from inert devices that were designed to be ignored by the body, to devices which were designed to control tissue response and integration. This definition has evolved and broadened to become the definition of tissue engineering. In the early 1990s Langer and Vacanti further defined tissue engineering as an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain or improve tissue function[3]. Tissue engineering captured the narrative for about a decade, but as restorative approaches moved from the laboratory to the patient more researchers have begun to call their work regenerative medicine. The emergence of stem cells with their promise of restoring function to diseased organs and tissues has provided much of the impetus to shift the emphasis away from tissue engineering toward regenerative medicine. Today, tissue engineering and regenerative medicine are used interchangeably, and although tissue engineering is really a subset of the broader field of regenerative medicine, the NIH definition of tissue engineering / regenerative medicine is 'an emerging multidisciplinary field involving biology, medicine, and engineering that is likely to revolutionize the ways we improve the health and quality of life for millions of people worldwide by restoring, maintaining, or enhancing tissue and organ function' (http://www.tissue-engineering.net/).

Where does dentistry fit into the field of regenerative medicine? Based on the fact that regenerative medicine's goal is to restore function to damaged organs and tissues, it is apparent that dentistry, which has long embraced the concept of restoring function of damaged teeth, has embraced this goal from the very beginning.

The field of regenerative medicine, as it currently exists across all the disciplines of biomedicine, is being partly driven by the use of stem cells or existing cells from the body. However, in addition to the cells, it is utilising synthetic materials, harvesting biological extracellular matrix, using growth factors and cytokines, and combinations of these to try to affect the

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goal of reconstituting tissue and organ function wherever that might be. In dentistry, the principal organ needing regeneration is the tooth along with the surrounding hard and soft tissue affiliated with the tooth. In a broader sense it includes oral and facial soft tissues like mucosa and the facial muscles. Which areas of dentistry are poised to use or already use regenerative medicine? We believe that virtually all of dental practice embraces the concepts and practices of restorative medicine.

So, has dentistry been part of the regenerative medicine paradigm since before its inception? Few medical specialties are as focused on the restoration of organ and tissue function as dental medicine, which currently uses a full range of the concepts of biomaterials, biomedical engineering, tissue engineering, and regenerative medicine to treat patients.

It is our opinion that, if you take as the primary criterion the restoration of tissue and organ function, dentistry has not only been at the forefront of restorative medicine but actually predates it in practice. The development of restorative materials, including amalgam fillings, has been focused on restoring teeth and thus organ function for many years prior to the definition of restorative medicine. Progress in this field has continued with the development of composite restorations that have greater aesthetic appeal, implants, and the development of materials to stimulate bone regeneration. Dentistry has undeniably been at the forefront of functional restoration, even before the fields of tissue engineering and regenerative medicine were defined.

Presently, dentistry continues to be a major player in the design and engineering of materials that will stimulate tissue repair. This includes implant dentistry, bone augmentation and repair and the use of stem cells for the regeneration of a host of hard and soft tissues that are important in head and neck regenerative medicine.

The depth and breadth of dental regenerative medicine can be demonstrated using examples of therapies or potential therapies from our laboratories at New York University. These begin with an example from a historical area of strength, dental implant design and fabrication, progress to a more high tech bone scaffold fabrication project and finish with a stem cell-based soft tissue engineering project.

DENTAL IMPLANTS

Surface engineered dental implants - regenerative medicine in clinical use

Dental implants have become a popular and successful approach to restoration of function of lost teeth. Their success is based on their ability to integrate in bone and soft tissue, although the importance of soft tissue integration, until recently, has not been recognised or adequately addressed. Since dental implants are one of the few medical devices that are permanent and transcutaneous, integration of epithelium and fibrous connective tissue are important to form a seal against the oral environment. In order to enhance bone integration, the dental implant industry has taken a largely empirical approach and used surface roughening techniques to enhance bone integration (osseointegration). This approach has worked using a variety of abrasive blasted, acid etched, and other processed surfaces, but there has been little organised scientific effort to determine how surface modification influences bone integration, or how to optimise surface design and fabrication. We have taken a regenerative medicine approach to this problem.

We know that local tissue response to surgical implants is based largely on cellular response to the implant surface during the healing process. When a cell comes in contact with the surface of the implant, that surface becomes extracellular matrix to the cell. The implant surface is always coated with proteins from blood and tissue and thus cellular response is to the local proteins and to the micro and nanostructure of the surface. The goal of an ideal implant is where the implant surface controls the behaviour of attached cells. In the optimal situation the implant surface would control cellular proliferation, cell shape, and differentiation, and yield soft and hard tissue response that is controlled resulting in tissue integration and function very much like the intact organ, thus fulfilling the goal of regenerative medicine. In order to develop a surface with these characteristics we began by conducting a series of experiments that examined bone and soft tissue cellular response to physical cues through a micrometre scale range.

Development of regenerative engineered implant surfaces

We conducted a series of studies examining cell response to controlled microstructure surfaces produced using microelectronics technology. The most effective surfaces we tested comprised repeat-pattern microchannels in a very specific size range. Growing cells on these microchannels controlled the shape and proliferation of the cells and inhibited colonisation and growth, whereas those grown on smooth surfaces in tissue culture resulted in cells that spread and migrated in uncontrolled directions and proliferated at high rates[4–6]. Optimal microchannel size for the inhibition of fibroblast growth and migration was determined to be in the 6–12 μm range in width, with repeat spacing of 12–24 μm, with the structure heights being greater than 2 μm.

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Based on this information we began researching methods for producing controlled microstructure on metal implant surfaces. We developed methods for using a pulsed Excimer laser with a comb mask system that produced consistent microchannel patterns on titanium alloy surfaces. The size and depth of the microchannels was controlled by the mask configuration and the number and duration of the laser pulses. The resulting surface has microchannels and superimposed micro and nanostructure, produced as the laser method melts titanium alloy in the microchannels and it solidifies on the ridges (*Figure 1*). Two configurations (8 μm and 12 μm feature sizes) of laser micromachined surfaces were then tested using an implantable chamber system in dogs to examine soft and hard tissue response and compare them to standard roughened surfaces[4,7]. The results showed that the microchannel surfaces developed earlier and more extensive bone attachments than the standard surfaces, and controlled the organisation of attached bone[7].

These laser microchannel surfaces were then applied to the collars of experimental dental implants. They were placed in a 2 mm wide band on the collar portion of the implants, where they exit from bone through fibrous tissue and epithelium, into the oral cavity, with the microchannels oriented circumferentially around the collar. In dog studies these surfaces were found to attach bone, fibrous tissue, and epithelium. They prevented epithelial downgrowth and crestal bone loss[8].

Clinical application of laser micromachined surfaces

These surfaces were used on implants manufactured by BioLok International (Deerfield Beach, FL). They were first used in human trials in 2000, and were approved by the US Food and Drug Administration in 2004. At that time they represented the first tissue engineered surface on an implant that was approved by the FDA.

The laser machined technology, referred to as Laser-Lok, was patented through New York University, before it was applied to the BioLok implants. BioLok became part of BioHorizons Inc., in 2006, and the Laser-Lok surface has now been applied to four BioHorizons implant systems. Three-year clinical studies, initiated by BioLok and published in 2009 showed that these implants developed surrounding tissue structure similar to stable biologic width (the normal connective tissue arrangement found around teeth) and prevented more than two-thirds of the crestal bone loss seen around implants without the Laser-Lok surface[9]. A human histological study also confirmed the results observed in the animal studies, that the Laser-Lok surface attached bone, fibrous connective tissue, and epithelium, stopping the epithelial downgrowth observed around most implant systems[10]. This study also showed the extent of fibrous tissue attachment to this tissue-engineered surface, which has not been observed on any other implant surface. While most roughened implant surfaces show little fibrous tissue attachment and exhibit a parallel collagen fibre scar capsule, this surface shows cells within the microchannels and a tangential collagen fibre arrangement (*Figure 2*). An additional clinical study[11] has further confirmed these results regarding bone and soft tissue attachment, prevention of crestal bone loss, and establishment of stable gingival aesthetics, the normal looking gingival soft tissue attachment seen around and between teeth.

Putting grooves on implants is not new in implant dentistry and there are a number of high quality implants in the field that have microthreaded collars. However, these are not identical to Laser-Lok. They were not engineered with regenerative medicine in

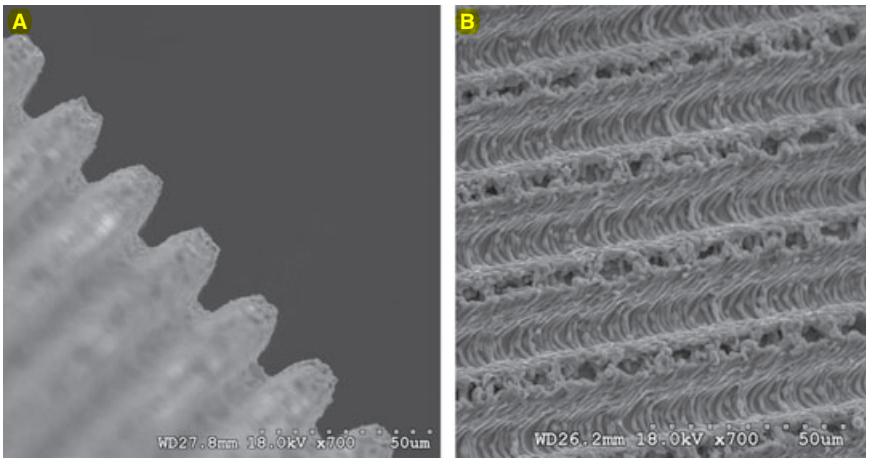

Figure 1. Scanning electron microscope images of the Laser-Lok surface showing a profile view of the microchannels (A) and a surface picture of the microchannels (B). Mag = 700×.

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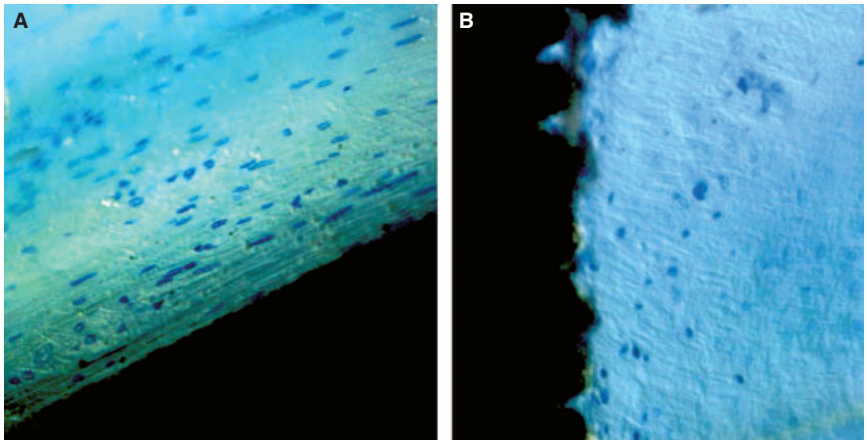

Figure 2. Interference microscopy photomicrographs of soft tissue adjacent to a roughened surface (A) and a Laser-Lok surface (B). The parallel collagen fibres and flattened cells at the roughened surface indicate formation of a scar capsule. The fibres oriented at an angle away from the Laser-Lok surface (tangential fibres) and the varied cross-section cells indicate the lack of an organieed scar capsule and the presence of a complex fibrous tissue attachment. Original magnification = 300×.

mind, and the grooves are not in the same order of magnitude as the very small 8–12 μm channels on the Laser-Lok surface as they were not designed to act on a cellular level. For this reason, the other implants do not affect cellular behaviour to the same level. The Laser-Lok implant design is based on regenerative medicine concepts that have been highly successful and has led to better regeneration of the soft tissue and bone around the restoration. This has changed the paradigm of implant surface technology, and demonstrated that cell and tissue response can be controlled at the implant interface, using regenerative medicine-based concepts.

SCAFFOLDING USE IN REGENERATIVE MEDICINE

Scaffolds play an important role in dental regenerative medicine, and they are more commonly used than is perceived. For example, all bone grafting materials and bone graft substitutes are scaffolds. They are not simply structural, but are often designed to act as a template for tissue formation. Cell and tissue response to a scaffold depends upon the composition of the scaffold, its surface microstructure, and its three-dimensional architecture. The cellular microenvironment at the interface between tissue and scaffold is extremely important and must be created to either recruit cells into the scaffold or allow cells to be seeded or transplanted for repair. In scaffold design the primary concerns are the surface condition of the scaffold, volume of scaffold versus space and the connective arrangement of the solid structural elements of the scaffold. If the surface is a coating of extracellular matrix (ECM), do the cells then secrete ECM; or do you incorporate ECM receptor binding sequences, integrin-binding domains, into your scaffold? Do the cells themselves respond and express different integrin receptors and can you facilitate migration, which would be the desired case in bone, just as we inhibited migration in the case of an implant collar?

The ideal scaffold for a particular tissue depends on the structure and properties of the tissue to be regenerated. First, the material must be nontoxic and biocompatible. A scaffold needs appropriate three-dimensional architecture; it needs to have appropriate physical and chemical stability so it will be retained in the body for the proper period of time, and it needs the right porosity and pore structure to accept and organise the types of cells and tissues you are trying to regenerate. It needs to be able to have the mechanical properties that are appropriate for the cells and their macro- and microenvironments. It needs to promote healing and it should not be so difficult to fabricate that it is not commercially feasible to produce.

Researchers have tried many different scaffold materials both in dentistry and in other areas of regenerative medicine. The most popular are collagen[12] due to the fact that it has been FDA approved in many medical device forms, and it is the most ubiquitous component of the ECM. Other naturally occurring components[13] are: laminin, the basement membrane component, fibrin, because it is easy to isolate and plentiful, and matrigel because it has proven to be so useful in tissue culture experiments. However, what has become very popular in soft tissue regeneration is to use decellularised natural organ matrix[14].

Scaffolds for bone regeneration

In the case of bone regeneration, there are three acceptable ways that bone can respond to a material. One is osseointegration, the best example of which is the metals that are used in implant dentistry, where the bone accepts that the foreign material grows very closely to the surface, but does not physically or

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chemically attach to it. The second, osseoconduction, is such that the bone physically attaches to and grows along the material surface and into pores in the material. Decellularised bone or synthetic hydroxyapatite materials work in this way. Osseointegration and osseoconduction can only occur from existing vital bone. Osseoinduction is the third way that bone can respond to a material. Osseoinduction is the stimulation of bone formation independent of existing bone, and only occurs because of molecular signalling, either from molecules inherent to native bone, or from addition of these molecular signals to a scaffold. Bone morphogenetic proteins (BMPs) cause osseoinduction to occur. The combination of osseoconduction and osseoinduction is the ideal approach to replacing bone, and is often observed when autogenous bone or combinations of mineralised graft and BMPs are used in scaffolds. This combination is capable of regenerating bone across large distances.

CURRENT BONE GRAFT MATERIAL

Available materials include human allograft materials, bone morphogenic proteins and bone morphogenic protein-containing materials, and xenogenic bone materials. There are a variety of calcium salt-based materials and bioactive glasses that can be used in various forms for shaping bone. A bone graft substitute material, human demineralised allograft bone, comes from a number of sources and tissue banks that provide them. It can both osteoconduct and osteoinduct bone. However, these materials may present an emotional incompatibility if a patient does not want cadaver bone put into his or her body. Xenogenic bone material must be treated so that only the mineral portion of the bone remains. There cannot be any connective tissue, or growth factors retained or else there could be an immunogenic response to the foreign proteins. For some patients, there is an appeal to the fact that it is not human, but this material has a drawback in that it can only osseoconduct bone.

Because of the shortcomings of the decellularised, deproteinated, biological materials, the quest for a synthetic material that has many of the properties of decalcified, decellularised bone has been conducted. Synthetic hydroxyapatite ceramic was developed in the 1970s for dental applications[15]. It is a material that will directly bond to bone and exhibits osseoconductivity. Because of that, many different forms have been created; it can be made in blocks or particulates, it can have cement so that it can be sculpted and added. Other calcium salt materials have evolved; tri-calcium phosphate, calcium carbonate and calcium sulphate; all of which have advantages and disadvantages, but do not fulfil the architectural requirements of bone even though they eliminate many of the shortcomings of the allograft material[16]. To date, the artificial scaffold materials that are in current usage are those that come in particulate form. Practitioners like particulate material since it can be packed into defects, but it needs to be stabilised with some sort of carrier or defect filling material. Coral or other solid forms in blocks need to be carved to fit a defect, and generally have the limitation of not having porosity that permits easy access of cells. Ideally practitioners would like to have an injectable hydrogel as a scaffold. This would be especially practical in an office, where the compounds would be mixed and injected and at body temperature would polymerise and fill the defect. Thus the defect could be repaired either in the office or the operating room. The hydrogel could be mixed with growth factors or other osseoinductive materials. Although there has been progress with hydrogels in other areas, there has been very limited success in the bone field due to the burden of mechanical properties needed for bone.

Requirements for repair of craniofacial bone are complex because of its complex architecture. Since no current graft materials can be fabricated in the complex shapes needed for, for example, cleft palate repair, scientists are looking to make more user-friendly forms to repair these complex defects. There are a number of different ways to fabricate the materials needed. These include gas-forming polymerisation solvent casting, freezing and drying materials to generate pores, electrospinning, and 3-D printing[17]. The new fabrication techniques all strive to permit the appropriate pore size and shape, distribution and connectivity between pores to be controlled in a way that the result acts as an effective scaffold for bone regeneration, stimulates osteoconduction and can be incorporated with growth factors that can induce osseoinduction or with cells that will induce osseoinduction. 3-D or Direct Write (DW) printing of bone replacement materials appears to have the greatest promise since one can control form and function[18] and add osteoinductive molecules to create a replacement material that has all the features that one looks for in a bone repair scaffold.

We have taken the DW approach to scaffold production for bone repair because the process can be computer controlled so that at room temperature we can create very intricate patterns of artificial materials; examples of these can affect the porosity, density and interconnectivity and can repair critical sized defects (*Figure 3*). These scaffolds can be custom printed to fit complex defects. The goal is to create a scaffold with prescribed features, filled with resorbable material that would eliminate the voids that allow for bacteria or blood-borne materials to become stagnant or coagulated. The scaffold will have time-release of antibiotics, growth factors, or drugs that would promote angiogenesis and control for the turnover and resorption of materials. To date we have designed scaffolds that have

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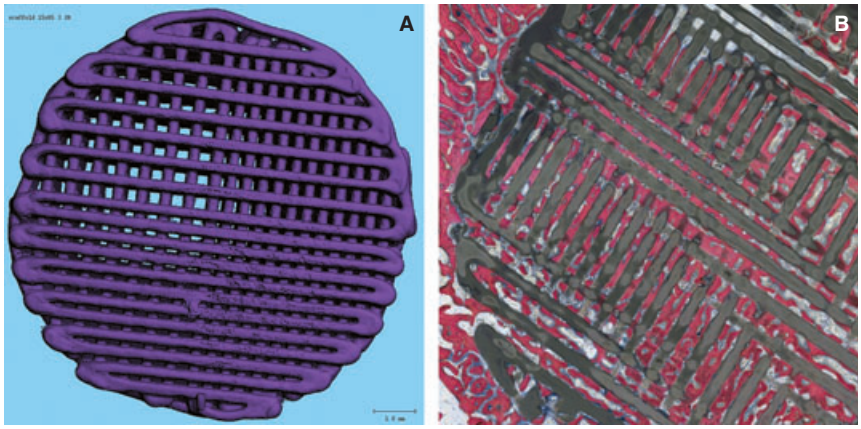

Figure 3. MicroCT reconstruction (A) of a DW scaffold showing the layered printing process, strut size, and variable lattice spacing parameters in different areas in the scaffold. Bar = 1 mm. Light histomicrograph (calcified) of bone and soft tissue formation in a DW scaffold at 8 weeks post implantation (B). The red-stained tissue is mineralised bone. The photomicrograph shows that different regions and spacings of the scaffold have different amounts and arrangements of bone structure. The irregular surfaces of some of the lattice struts (grey) indicate osteoclastic resorption. Strut diameter = 267 μm on average.

variable porosity and permit bone in one region but restrict soft tissue ingrowth[19]. We have also made these from different combinations of hydroxyapatite and tricalcium phosphate that have different remodelling rates. Some of these are permanent[19] while others have been shown to regenerate bone and remodel by osteoclastic resorption (*Figure 3*) exhibiting the potential to leave only regenerated bone. These have potential for use in paediatric applications where growing craniofacial bone prevents use of permanent scaffolds. In animal studies, these scaffolds have demonstrated different amounts and configurations of bone formation, depending on the spacing of the struts of the scaffold, and scaffolds can be printed that generate either trabecular bone patterns or cortical-like structures, each of which have different remodelling rates. So, these scaffolds can be printed and can regulate type and density of bone formation as well as scaffold turnover.

What is the future of this technology? Many plastic surgeons are already using virtual reality assisted surgery where MRI and CAT scan images in trauma and reconstructive cases are used to design the replacement of hard tissue analogue structures prior to entering the operating room so that they can have exact reconstructive replicas to work with. One can envisage Direct Write technology interfacing with this technology in much the same way CAD-CAM has changed dental crown fabrication. Based on MRI and CAT scan data, custom bone and soft tissue scaffolds could be fabricated on a case-by-case basis.

The future of scaffolds and bone repair is such that 3-D printed Direct Write scaffolds with bone conductive zones and barriers to soft tissue have been created and successfully tested in animal models. We have been able to match the size of the individual struts of these scaffolds to the size of ingrowing trabecular bone. The resulting scaffolds effectively conduct bone along great distances. We have also created multiphasic scaffolds, containing soluble carriers, temporary reinforced materials, and bioactive molecules. In the near future they may contain hydrogels, and eventually, stem cells or other live cells. It is anticipated that forms of this technology will be in clinical trials in a few years.

STEM CELLS

So, what does the future hold for regenerative medicine in dentistry? As in all areas of medicine, stem cells will dominate, but in dentistry more than other areas, it will be coupled with the use of substrates, scaffolds, and growth factors. This is due in part to the major role the components currently play in regenerating oral structure and function. However, the field will be driven as major strides take place in stem cells. The sheer activity around stem cells and the growth of the field will indicate where the future of regenerative medicine goes. In dentistry, the initial buzz was the attempts to grow a tooth using stem cells. Although we think that someone will do that, one has to ask the question, will this ever be available for the practising dentist[20,21]? If it is, would patients elect to grow a new tooth that will still be vulnerable to decay and the same problems that they had with their existing teeth? We predict that the answer will be 'no'. Growing teeth from stem cells would have utility in congenital conditions where there is agenesis of teeth, but as a restorative therapy it will only happen if the technology advances to where one can grow a mature tooth in a matter of months and not years. However, stem cells should prove useful for the regeneration of pulp to save teeth,[22] for the regeneration of periodontal ligament and bone[23] and for re-anchoring teeth to prevent tooth loss in periodontal disease. Regenerating soft tissue using stem cells

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including oral mucosa and muscle for reconstruction of lost craniofacial muscle both have a higher likelihood of success in the future than regenerating a tooth.

Sources of stem cells

There are a variety of sources of stem cells. The source that gets the majority of press coverage is embryonic stem cells[24]. In the USA, their use was banned, then allowed in a limited fashion, then expanded and now there are lawsuits to reduce the use again. Embryonic stem cells are very important to the field of regenerative medicine, but the controversy has forced scientists to look at the alternatives available. Adult stem cells have been found in almost every tissue, and there are researchers looking for them in the remaining tissues[25]. One area that has received a lot of attention is the isolation of stem cells from adipose tissue[26]. In most parts of the world, patients needing regenerative medical treatment have an excess of adipose tissue that can be used to harvest stem cells. In a way this can be viewed as a biorepository of stem cells.

Technology is driving ways to harvest and store a variety of stem cells. There are stem cell banks to store cord blood and dental pulp stem cells for future use. Dental pulp cells have great utility in dentistry and have been shown to differentiate into all the cell types needed for regeneration of teeth and related structures[22]. One could see parents arranging for stems cells to be harvested from their children's deciduous teeth and saving them for future treatment of dental and non-dental regenerative medicine therapies. The most recent addition to the list of stem cells is the induced pluripotential stem (iPS) cells. These stem cells are created from fibroblasts by the transfection of four genes which alter the phenotype of fibroblast-like cells to cells with an embryonic stem cell-like phenotype[27]. Like embryonic stem cells, the appeal of iPS cells is that they have the highest level of pluripotency. They can derive into every cell type, they are unlimited in self-renewal, have enhanced polymerase activity and do not age or lose their self-renewal capabilities. The downside is the fear of teratoma formation. Because they need to be grown with serum and other components, they may contain animal pathogens and can elicit an immune response.

The advantages of adult stem cells and iPS cells are that they clearly do not have the same ethical issues as embryonic stem cells and they are immune privileged since they are derived from the patient seeking treatment. One of the most overlooked areas in the specialised area of reconstructive head and neck surgery is soft tissue reconstruction and in particular, muscle. Patients with defects and loss of muscle are predominantly presenting following surgical removal of head and neck tumours or from injury or trauma, with battlefield-related injuries being the most common of these.

Our laboratory has taken the approach of using the stem cells that exist in every patient's skeletal muscle as a source for regeneration of lost skeletal muscle[28]. These stem cells are known as satellite cells because they sit outside the muscle cell but inside the basement membrane of the skeletal muscle cell, in a satellite position. Satellite cells are dormant until skeletal muscle is injured and then they can fuse with the injured muscle and aid in repair. Thus they are a perfect source of cells for a regenerative medicine approach to replacing lost skeletal muscle.

Just as we described using patterning of titanium to instruct cells to assume a desired shape and pattern in order to achieve a tissue-like pattern of cells a regeneration of the soft tissue around implants, the same approach is being used with muscle stem cells. We pattern collagen in such a way that the cells attach, find each other, fuse, and give rise to elongated skeletal muscle cells (*Figure 4*). Then these myotubes can be grown under conditions that allow for multi-layering. These muscles look and behave like muscle *in vivo*, although small[28]. We have been able to develop

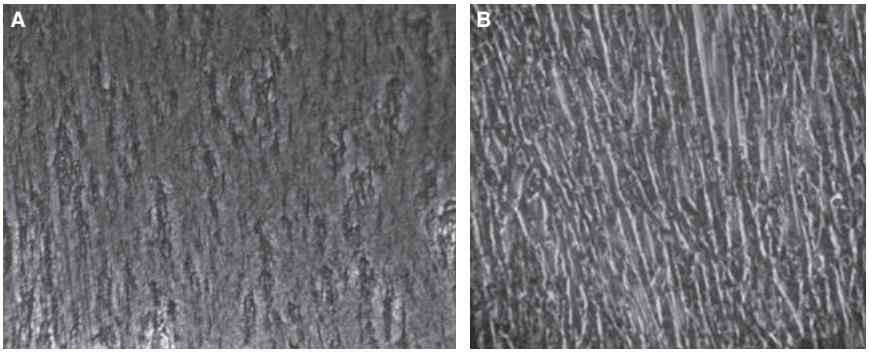

Figure 4. Phase contrast micrographs of an aligned collagen gel without cells (A) and plated with human satellite cells (B). The satellite cells attach to the collagen and align in the oriented groves of collagen. These cells fuse into multinucleated myotubes (←) that have many of the characteristics of muscle *in vivo*. Magnification 80×.

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collagen scaffolds that have a pattern that resembles skeletal muscle and have the physical and mechanical properties necessary for soft tissue and the compliance and resiliency of muscle. We have been able to grow our cells on these scaffolds and then transplant them into animals to replace lost muscle[29]. The next phase of this work will be to scale up to a large animal and to develop the procedures using human satellite cells. To date the results are very promising.

CONCLUSIONS

The main focus of dentistry, to restore function of teeth, has marked dentistry as a leader in regenerative medicine/tissue engineering, since before these fields were defined. While the original mission of dentistry was limited to restoration of function of teeth, this mission has greatly expanded in recent years, to include restoration of function of the full range of craniofacial structures and tissues. As dentistry's mission has become more complex, the regenerative medicine solutions have also become more complex, leading to some of the therapies and potential therapies outlined in this paper. We expect dentistry to stay at the forefront of regenerative therapy because it is in the craniofacial arena that many of these therapies will see their first clinical application. Bone repair therapies, for example, will be tested and developed in the craniofacial arena before they are used in areas such as orthopaedics, because of the accessibility of the oral cavity and relatively smaller and less load-bearing nature of craniofacial bone defects. Biomaterials have traditionally been tested in the dental and craniofacial fields before being utilised in other medical specialties, and we expect that tissue engineering scaffolds for many types of tissues will follow similar development pathways. The restorative nature of dentistry will keep it at the forefront of regenerative medicine.

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Conflicts of interest

The authors declare no conflicts of interest.

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