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RESEARCH ARTICLE

APPLICATIONS OF TISSUE ENGINEERING IN ORAL AND MAXILLOFACIAL SURGERY

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ABSTRACT

Introduction: Engineering of craniofacial tissues will have a profound impact on treatment strategies and surgical modalities in the future. Millions of patients across all ages are affected annually by sequelae of aberrant development, trauma and disease. Tissue engineering is a relatively new interdisciplinary field that seeks to provide a unique solution to tissue loss or deficiency. This involves implanting specific population of autologous living cells that have been isolated, expanded in tissue culture and introduced into scaffolds like a polymer framework. The concept of conscripting patients' own cells to rebuild lost or damaged tissue is the basis of several novel tissue engineering techniques. The future will see rehabilitation strategies shift from prosthetic to regenerative. The paper discusses the scope and applications of tissue engineering in the field of oral and maxillofacial surgery along with its utility in clinical dentistry. It reflects on how close partnerships between basic and clinical scientists are imperative to revolutionise our field.

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INTRODUCTION

Tissue Engineering may be defined 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 or a whole organ" (Langer, 1993). The reconstruction of large tissue defects is one of the main challenges to face the modern oral and maxillofacial surgeon (Payne, 2014). Fundamentally this involves combining biochemical/biomaterial engineering with cell transplantation to create artificial tissues and organs (Sterodimas, 2009). The main aim of developing this technique is to be able to use the patients' own cells to replace the lost or injured tissue. This reduces graft morbidity and improves the viability of reconstructive procedures. Oral and maxillofacial surgeons are frequently faced with defects in the jaws resulting from periodontal disease, trauma and pathologies/tumors. Prosthetic rehabilitation has been the norm but in recent years regenerative techniques have been gaining popularity. When shifting rehabilitation strategies from prosthetic to regenerative—such as with a tissue engineering approach—one must deal with the uniqueness of the craniofacial structures in their development and function (Patil, 2016).

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Soft Tissue Applications: Oral Mucosa

One of the principal reasons for development of a tissue-engineered human oral mucosa is for the treatment and closure of surgical wounds. Other potential uses are: in vitro models to study the biology and pathology of mucosa, as a vehicle for delivery and expression of transduced genes (gene therapy), and as an alternative to animals for safety testing of consumer products in an in-vitro system (Boyce, 1996). In development of a tissue-engineered oral mucosal equivalent, two basic components are necessary: the superficial portion or epidermis that contains the keratinocytes and the deeper portion or dermis. Previous investigators have attempted to graft skin and oral mucosal defects with epithelial sheets (Gallico, 1984; De Luca, 1990; Lauer, 1994; Hata, 1995 and Raghoebar, 1995). These epithelial sheets are friable and difficult to handle with a low engraftment rate. Parenteau *et al*. (Parenteau, 1991), demonstrated that the rate of closure of the wound and the increase in percentage of wound repair are enhanced with the presence of a dermis. Clugston *et al*. (Compton, 1993), noted that the absence of a grafted dermis resulted in a contracture of cultured keratinocyte auto-grafts by approximately 50%. The development and grafting of a dermis can assist in epithelial

graft adherence, minimize wound contraction and assist in epithelial maturation while encouraging the formation of a basement membrane (Inokuchi, 1995).

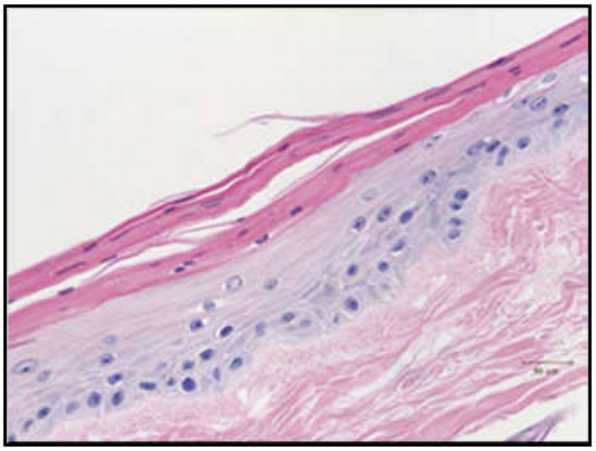

Fig. 1. H&E stained section of AlloDerm demonstrating polarity of dermal matrix

In order to resist shear stresses placed on it, the epithelia should form a continuous basement membrane with a basal lamina and an anchoring zone (Clugston, 1991). Nanchahal and Ward, in their review of the literature, thought that a major drawback of the available cultured composite skin grafts was their poor handling characteristics (Nanchahal, 1992).

dermal matrix that is instructive and communicative with the cultured oral keratinocytes. A non-immunogenic, biocompatible, acellular cadaveric human connective tissue matrix known as AlloDerm has been developed by LifeCell Corp. The dermal matrix has a polarity with an intact basement membrane on one side, which allows keratinocytes to form desmosomal attachments, and open "pores" within the reticular tissue on the other side, which allow cellular migration to occur. (Fig. 1) It has consistently been shown to integrate into the host tissues. AlloDerm also contains intact vascular channels that serve as conduits for endothelial cell migration to occur, thus establishing a more rapid revascularization of the free mucosal graft. Furthermore AlloDerm trims, adapts and sutures like autologous tissue and thus is "surgeon friendly" in its handling characteristics (Livesey, 1995). A pilot clinical trial was concluded at University of Michigan (Proof of Concept) using the human ex-vivo produced oral mucosal equivalent (EVPOME) (Izumi, 2013). The manufacture of EVPOME in the Human Applications Laboratory, which is in the General Clinical Research Center, is done under current good manufacturing practice standards for grafting into subjects in need of periodontal surgery (Fig. 2). In another study to assess the efficacy of EVPOME for intraoral grafting procedures, autogenous keratinocytes were harvested from a punch biopsy 4 weeks prior to surgery, placed in a serum-free culture system and seeded onto a human cadaveric dermal equivalent, AlloDerm.

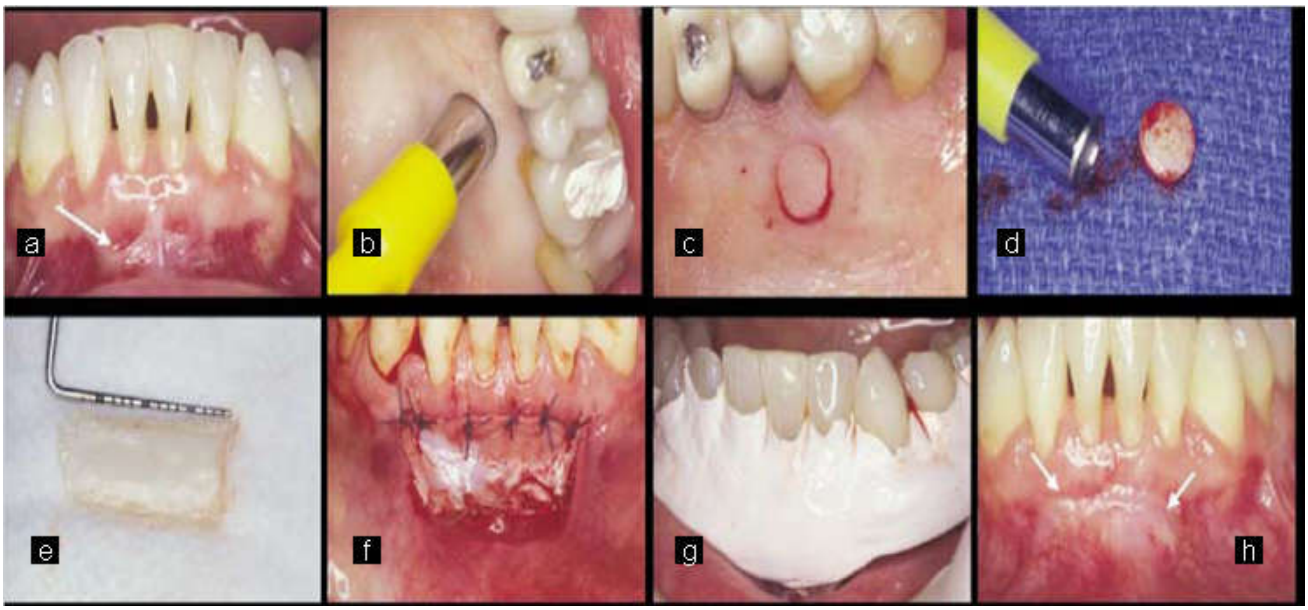

Fig. 2. a- Defect in attached mucosa, b,c- Punch biopsy taken from keratinized mucosa of palate, d- Tissue isolated and subsequently soaked in trypsin to dissociate oral keratinocytes, e- Prepared EVPOME prior to transplantation, f- Securing and suturing the graft to the defect, g- Graft covered with a periodontal dressing, h- Postoperative results

It was believed that the dermal component needed improvement in its tensile strength as well as in the production of a lamina densa and anchoring fibrils. A dermal equivalent would be best made out of human collagen as it would help to promote deposition of additional basement membrane constituents and show a better pattern of keratinocyte differentiation and less immunogenicity as compared to one constituted with animal collagen (Auger, 1995). The ideal mucosal graft should be constructed of autogenous oral keratinocytes grown in a serum-free or defined medium without a xeno-genic feeder layer. Prior to grafting into the oral cavity, the oral keratinocytes should be applied to a human

Thirty patients with either a premalignant or cancerous lesion were triaged into 2 groups, depending on the stage of disease: group 1, EVPOME, or group 2, AlloDerm, control without an epithelial layer. Clinically, EVPOME grafts were easy to handle and showed excellent compliance on grafting (Fig 3). Both EVPOME and AlloDerm grafts showed a 100% take rate. At 6 days post grafting, the EVPOME clinically showed changes indicating vascular in growth and had cytological evidence of the persistence of grafted cultured keratinocytes on the surface. They had enhanced maturation of the underlying sub-mucosal layer associated with rapid epithelial coverage compared with the AlloDerm grafts at biopsy samples taken at

28 days post-grafting (Izumi, 2003). In summary, EVPOME appears to be an acceptable oral mucosal substitute for human intra-oral grafting procedures and results in a more favorable wound healing response than does AlloDerm alone. Clinical uses for a tissue-engineered oral mucosa would include repair of intra-oral mucosal defects that were acquired (trauma, pathology, etc) or congenital (clefts) and certainly even some extra-oral defects (eyelids/conjunctiva or nasal). The development of a composite oral mucosa equivalent will offer the surgeon not only a material to assist in reconstruction of the oral cavity but also a means to introduce the concept of somatic gene therapy. This emerging technology holds great promise for the treatment of both inherited (diabetes, hemophilia) and acquired (oral cancer, osteo-radionecrosis) diseases (O'Malley, 1993).

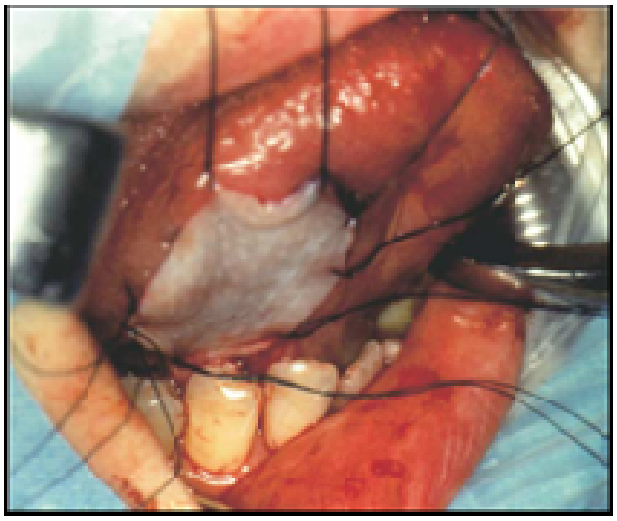

Fig. 3. EVPOME graft sutured intra-orally

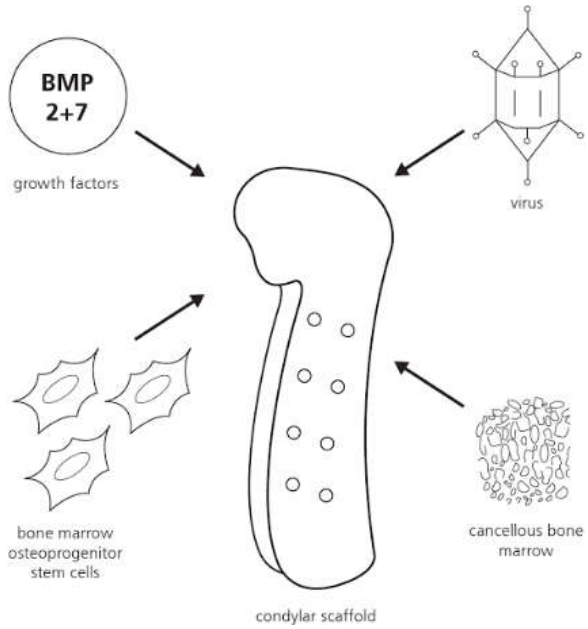

Fig. 4. Various biologics involved for creation of a composite scaffold

Hard Tissue Applications

Research into hard tissue scaffolds has clear significance to oral and maxillofacial surgery. The ultimate goal of regeneration is to provide esthetics, minimize scarring and maximize function across all fields. To accomplish this task effectively, several principles must be adhered to, and these may vary between reconstruction of hard and soft tissues (Flock, 2005). Ideally, scaffolds must have physical properties that are similar to the native material they are replacing. This means not just "bone," but "mandibular bone" or "mandibular condyle." For some applications, a combination of these materials and techniques may offer the best and most accurate reconstruction (Fig 4). Base scaffold materials being investigated include polymers, ceramics, and metals (Chu, 2002).

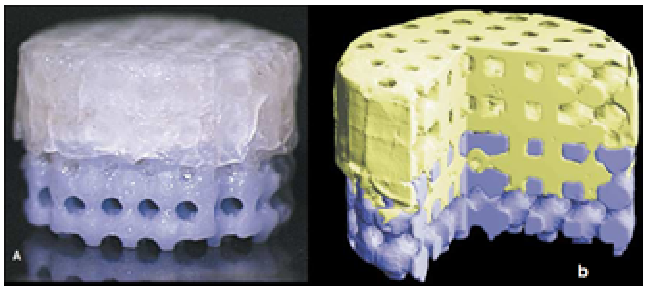

Fig. 5. Different osteo-conductive materials bound to a scaffold to confer beneficial properties for bone regeneration and cartilage formation

Ridge augmentation and replacement of alveolar bone

Bone augmentation and regeneration related research is currently focused on molecular, cellular and gene therapeutics (Taba, 2005). Bone morphogenetic proteins (BMPs) are differentiation factors and have the ability to differentiate osteoprogenitor cells into mineral forming osteoblasts and stimulate vascular proliferation (Sheikh, 2015). However, optimal dosage and carriers for PDGF are still to be determined and extensive preclinical and clinical trials are required in future. A new approach to achieve bone augmentation is the addition of platelet rich plasma (PRP) from the patient blood to graft materials (Urist, 2013). Initial results have shown more and denser bone compared to auto grafts used alone for ridge augmentation procedures (Sheikh, 2013). The seeding of constructs with mesenchymal stem cells also holds great promise and merits further in-depth investigation (Farokhzad, 2006). Investigators are currently studying the potential therapeutic effects of growth factors and cytokines for regeneration of alveolar bone. Many of these factors stimulate regeneration of bone and influence bone growth and resorption. Animal studies have indicated that recombinant human BMP-2 (rhBMP-2) may have excellent therapeutic potential in ridge augmentation of maxilla, maxillary cleft repair and replacement of lost alveolar bone (Boyne, 1997). In conclusion, there is a need for a minimally invasive and refined technique for bone augmentation to increase the vertical height along with better biomaterials and pharmaco-therapeutical adjuncts.

Maxillary sinus augmentation and implants

The rehabilitation treatment with the use of dental implants has become increasingly mentioned because of their high predictability and being a more conservative treatment than conventional prosthesis (Priest, 1999). Implants require a good quantity and quality of bone support. To achieve this various grafting procedures and sinus augmentation surgeries have been done traditionally with varying degree of success rates. Studies that compared the synthesized materials for tissue

engineering with scaffolds (xenogenous or alloplastic) without activation of cells and/or growth factors showed that bio-activated scaffolds, presented higher success of osseointergration (Jiang, 2009 and Wang, 2011) and bone to implant contact (Gruber, 2009), when applied in maxillary sinus augmentation. This demonstrates that the application of tissue engineering technology adds to scaffolds the osteogenic capacity. Exogenous cells can be used as a key element for progressive bone formation in the maxillofacial region. Yoshikawa *et al*. have established the culture method of mesenchymal stem cell (MSC) from rabbit bone marrow (Yoshikawa, 1995). This technique can be used for the augmentation of maxillary sinus floor for dental implant surgery. A window is cut in the lateral wall of the maxillary sinus leaving the underlying mucosal membrane intact to place graft material in this area. MSC and b-TCP complex were used as a graft material to the maxillary sinus to provide sufficient volume of bone for dental implants. After bone augmentation, longer fixtures can be installed penetrating into the maxillary sinus. This can greatly contribute to occlusal reconstruction using implants in the dental field.

Temporomandibular joint

Cartilage tissue engineering in oral and maxillofacial surgery is limited very much to the Temporo-mandibular joint (TMJ). One of the major problems to overcome in tissue engineering of TMJ cartilage is the specific structural requirements of tissue engineered TMJ cartilage to withstand the in vivo forces as well as the fixation and connection of remaining ligaments (Melek, 2015). Thus, the characteristics of common hyaline cartilage that is used by many tissue engineering approaches to replace joint cartilage will not be appropriate to replace TMJ cartilage (Wang, 2007). Current research is focused to develop a mapped macro-structured template for the TMJ. The contra-lateral normal side can be used for a symmetric mirror image template design. Standardized templates can be inserted to reconstruct a defect or tissues can be computationally designed from scratch. Scaffolds generated from computer-simulated templates can be manufactured and secured to local tissues for stabilization and function (Yamamoto, 1997). A variety of internal micro-architectures can be applied to the scaffolds to allow variable degrees of porosity and strut structure based on interconnecting spheres or cylinders. The mandibular condyle is an example, where the bone portion might be reconstructed with a ceramic scaffold, while the articulating surface might be better served with a polymer scaffold (Fig 5), (Hibi, 2006).

Distraction osteogenesis

Mechanical stimulation is an important signal to activate tissue growth and regeneration. Distraction osteogenesis (DO) is characterized by the application of such a mechanical stress to the callus. It can provide predictable bone regeneration without grafting procedures but requires longer treatment time and forms less bone transverse to the direction of distraction. To promote 3D bone formation and shorten the consolidation period, tissue engineered osteogenic bone has been applied in a patient being treated with vertical DO and an osteo-cutaneous fibular flap to reconstruct the mandible. The material comprising of autologous mesenchymal stem cells, culture-expanded and platelet rich plasma activated with thrombin and calcium chloride was infiltrated into the distracted tissue at the end of distraction and injected into a space created labially with a titanium mesh. The infiltration contributed to full consolidation of regenerate for 3 months and the injection thickened the regenerated ridge and bridged a gap between the native mandible and the distracted fibula. The reconstructed mandible was expanded from 10mm to 25mm in height despite a lacerated and opened area in the distracted area (Yamamoto, 1997), Animal studies that have been carried out to confirm the possibility of new bone formation by DO have yielded promising results. Integration of the implants within the transport segment and the regenerated bone was observed. The regenerated bone consisting of mature lamellar and cancellous bone achieved osseointegration between implant and bone (Hibi, 2006). It is thus a promising tool in regenerative techniques.

Conclusion

We are in vanguard of new approaches to rationally understand disease progression and to develop novel therapeutic strategies. Further research is essential to bring any product to clinical use, and we are only at the beginning of understanding the complex cellular relationships promoting regeneration and modulating scarring. The field of regenerative medicine is here to stay as exemplified by several examples of translation from bench to bed side (Patil, 2013). Close partnerships between basic and clinical scientists are imperative to develop novel treatment modalities that will revolutionize oral and maxillofacial surgery!

Compliance with Ethical Standards

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Ethical approval

This article does not contain any studies with human participants or animals *performed by any of the authors.*

Informed consent

Informed consent was obtained from all individual participants included in the study. Identifying information of any of the subjects/participants is not included in the review paper

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