IJIRR

International Journal of Information Research and Review
Vol. 2, Issue, 02, pp. 407-411 February, 2015

Review Article

TISSUE ENGINEERING—AN EMERGING APPROACH IN PERIODONTICS

[1,*]Dr. Megha Phogat Rana and [2]Dr. Tarun Rana

[1]Department of Periodontics, Subharti Dental College and Hospital, Meerut, India
[2]Department of Orthodontics, Subharti Dental College and Hospital, Meerut, India

ARTICLE INFO

Article History:
Received 27th November, 2014
Received in revised form
20th December, 2014
Accepted 30th January, 2015
Published online 28st February, 2015

Keywords:

Tissue Engineering,
Periodontal Disease,
Scaling, Currettage,
Regeneration

ABSTRACT

Tissue engineering is a multidisciplinary field with the potential to replace tissues lost as a result of trauma, cancer surgery, or organ dysfunction. Periodontal disease leads to loss of periodontal supporting structures, like cementum, the periodontal ligament and the alveolar bone. Periodontal treatments like scaling, root planing and gingival curettage are effective in repairing disease related defects and halting further progress of disease. In recent years tissue engineering strategies for clinical applications have been mainly developed in different medical fields to replace skin, cartilage, bone, cardiovascular component and pancreas. It has been applied in dentistry mainly in the fields of oral and maxillofacial surgery and periodontics for bone and soft tissue regeneration. In this paper an overview of the basic principles of tissue engineering and its application in periodontics is explored.

INTRODUCTION

OVERVIEW

Tissue engineering was first proposed in the 1980s by a chemist, R. Langer and a surgeon, J. P. Vacanti (Langer, 1993). It first employs the knowledge of life sciences, for example, cell biology, molecular biology, biochemistry, for the growth and development of new tissues. It draws on advances in materials science and engineering to include current engineering design principles in the formulation of strategies to engineer truly functional tissues. The field then incorporates the therapeutic principles of medical and dental clinicians and surgeons in order to bring the scientific component to practical application (Shalak and Fox, 1988). Tissue engineering, according to National Institute of Health definition, is an emerging multidisciplinary field involving biology, medicine, and engineering that is likely to revolutionize the way we improve the health and quality of life for millions of people worldwide by restoring, maintaining, or enhancing tissue and organ function (Sipe *et al*., 2002). For periodontal tissue engineering, this specifically relates to repair of alveolar bone, tooth associated cementum and periodontal ligament (PDL) (Giannobile, 1996).

Corresponding author: Dr. Megha Phogat Rana,
Department of Periodontics, Subharti Dental College and Hospital, Meerut, India.

Tissue engineering is defined as the science of fabrication of new tissues for replacement and regeneration and is based on principles of developmental and molecular biology, signal transduction and cell biology, including the supramolecular assembly of the extracellular matrix or ECM.

TISSUE ENGINEERING TRIAD

The three key elements for dental tissue engineering are signals for morphogenesis, progenitor/stem cells, and scaffolds of extracellular matrix components.

- The key morphogenetic signaling families are BMPs, FGFs.
- The progenitor/stem cells include cells derived from marrow, dental pulp and PDL-derived cells.
- The extracellular matrix scaffold consists of collagens, fibronectin and proteoglycans, including hyaluronic acid. Synthetic foams, fibers, gels and membranes can be incorporated with biomimetic biomaterials.

The triad of signals, stem cells and scaffolds can be used for regeneration of bone, PDL, cementum and dentin. It is believed that growing tissues require an adequate vascular supply to ensure viability and an unencumbered physical space into which the growing tissue can expand.

A major complication and limiting factor in the achievement of periodontal regeneration is the presence of microbial pathogens that contaminate periodontal wounds and reside on tooth surfaces as plaque-associated biofilms (Slots *et al*., 1999).

STRATEGIES TO ENGINEER TISSUE

Currently, strategies employed to engineer tissue can be categorized into three major classes: *conductive, inductive and cell transplantation approaches. Conductive approaches* utilize biomaterials in a passive manner to facilitate the growth or regenerative capacity of existing tissue. An example of this that is very familiar to dentists, and particularly periodontists, is the use of barrier membranes in guided tissue regeneration. Nyman *et al.* (1982) were the first to successfully use osteoconductive mechanisms in providing a means for selective wound healing by supporting the ingrowth of the periodontal supporting cells, while excluding gingival epithelial and connective tissue cells from reconstruction sites (Nyman *et al*., 1982).

The second major tissue engineering strategy, *induction* involves activating cells in close proximity to the defect site with specific biological signals. The origins of this mechanism are rooted in the discovery of bone morphogenetic proteins (BMPs). Urist first showed that new bone could be formed at nonmineralizing, or ectopic, sites after implantation of powdered bone (bone demineralized and ground into fine particles). Contained within the powdered bone were proteins (BMPs), which turned out to be the key elements for inducing bone formation.

MULTIDISCIPLINARY ASPECT OF TISSUE ENGINEERING

The clinician is required in order to sample a small biopsy of tissue. This tissue is then taken to the laboratory and multiplied several millionfold. Principles of cell biology must be employed in order to grow these cells and sustain their function. Engineers manufacture the biodegradable polymer matrices and the tissue growth bioreactor in which the tissue will grow. Once the cells have been expanded to an appropriate number, they are placed (seeded) onto the polymer scaffold. The tissue is then allowed further growth in the bioreactor until time of transplantation by the clinician. After transplantation, the engineered tissue may continue to grow until completely developed. The bioengineer manufactures the tissue, in bioreactors, and the material onto which the cells will be placed for transplantation. Lastly, the clinician is required to transplant the engineered tissue.

After transplantation, the polymer scaffold degrades and/or is remodeled by host and transplanted cells, resulting in a completely natural tissue. A common feature to all three of the tissue engineering strategies is that they typically employ the use of polymeric materials. In conductive approaches, the polymer is used primarily as a barrier membrane for the exclusion of specific cells that may disturb the regenerative process. Inductive approaches typically employ a carrier or vehicle for the delivery of proteins (e.g., BMP) or the actual DNA (gene) that encodes the protein.

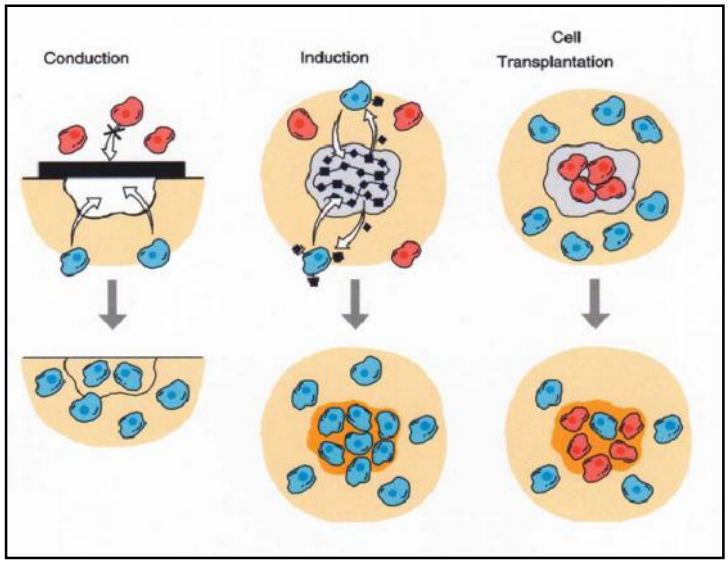

Figure 1. Strategies to engineer tissue

These proteins are now available in recombinant forms and produced on a large scale by biotechnology companies. One limitation of inductive approaches is that the inductive factors for a particular tissue may not know (Urist, 1965). In this situation the third tissue engineering approach, *cell transplantation*, becomes very attractive. This approach involves direct transplantation of cells grown in the laboratory. The cell transplantation strategy truly reflects the multidisciplinary nature of tissue engineering, as it requires the clinician or surgeon, the bioengineer, and the cell biologist (Krebsbach *et al*., 1999).

The two major types of polymeric materials used in all three tissue engineering strategies are collagen derived from animal sources and synthetic polymers of lactic and glycolic acid (same polymer used in resorbable sutures).

CLINICAL IMPLICATIONS OF TISSUE ENGINEERING

Tissue engineering will have a considerable effect on dental practice and the greatest effects will likely be related to the repair and replacement of mineralized tissues, the promotion of oral wound healing and the use of gene transfer adjunctively.

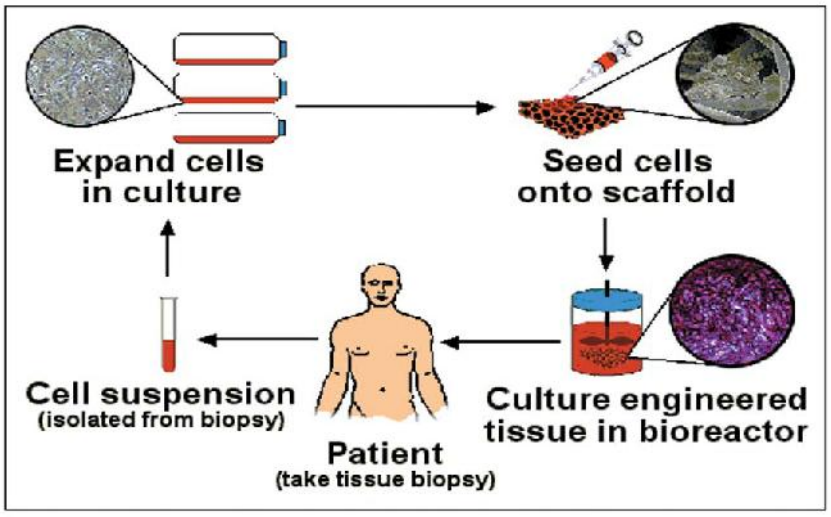

Figure 2. Multidisciplinary aspect of tissue engineering

This field is increasingly being viewed as having enormous clinical potential. Dentistry has continued to place considerable emphasis on the study and use of biocompatible materials. The purpose of this brief review is to provide the practicing dentist with a general perspective and background on tissue engineering, a sense of what has been accomplished in this field thus far, a consideration of the likely impact of tissue engineering on the practice of dentistry during the next 25 years.

BONE

Tissue engineering will likely have its most significant impact in dentistry via bone tissue engineering and regeneration. Bony defects secondary to injury, disease, and congenital disorders represent a major health problem. Current strategies aimed at replacing bony defects include the utilization of autografts, allografts, and synthetic biomaterials. Despite the fact that these substitutes restore stability and function to a reasonably sufficient degree, they still contain limitations. This has led to interest in engineering bone, which can be achieved using all three tissue engineering strategies. Both conductive and inductive approaches can be used to regenerate small bony defects. Guided tissue regeneration (GTR) after periodontal surgery represents a conductive approach to regeneration of bone. BMPs, related proteins, and the genes encoding these proteins allow one to engineer bone using inductive approaches in situations where GTR is not sufficient. In contrast, cell transplantation approaches offer the possibility of pre-forming large bone structures (e.g. complete mandible) that may not be achievable using the other two strategies. These structures may even be completely developed in the lab prior to use in large-scale reconstructive procedures (Alsberg *et al*., 2001).

SKIN AND ORAL MUCOSA

The most successful application of tissue engineering to date is the development of skin equivalents. Skin tissue is needed in adjunctive esthetic treatment of individuals who are severely disfigured following severe burns, in radical resective surgery to treat invasive cancers, and for major trauma wounds (like shotgun wounds and knife lacerations). Skin with both dermal and epidermal components is grown in the lab using a combination of cells and various polymer carriers.

The engineering and transplantation of oral mucosa and gingiva could be potentially important as a new technique in periodontal graft surgery and in the treatment of gingival recession (Parenteau, 1999; Naughton, 1999).

DENTIN AND DENTAL PULP

The greatest potential for engineered tissues is in the treatment of tooth decay. There are several ways in which one can potentially engineer lost dentin and dental pulp. There is now evidence suggesting that even if the odontoblasts (cells that produce dentin) are lost due to caries, it may be possible to induce formation of new cells from pulp tissue using certain BMPs. These new odontoblasts can synthesize new dentin. Tissue engineering of dental pulp itself may also be possible using cultured fibroblasts and synthetic polymer matrices (Nakashshima, 1990; Mooney *et al*., 1996).

CARTILAGE

Cartilage destruction is associated with trauma and a number of diseases including degenerative articular cartilage destruction at the temporomandibular joint. The limited capacity of cartilaginous tissue to regenerate and the lack of inductive molecules have focused interest among researchers and manufacturers in developing cell transplantation approaches to engineer cartilage. Transplantation of cells without a carrier is now used clinically to repair small articular cartilaginous defects. Investigators have also demonstrated in animal models that new cartilaginous tissue with precisely defined sizes and shapes relevant to maxillofacial reconstruction (e.g., nasal septum, temporomandibular joint) can be engineered using appropriate biodegradable scaffolds for transplanting the cells (Brittberg *et al*., 1994; Puelacher *et al*., 1994).

A LOOK TO THE FUTURE OF DENTISTRY

As described above, engineered skin tissue and cartilage are becoming available for certain medical applications and strategies to engineer bony tissues are close to receiving FDA approval. We foresee dental applications of these engineered tissues within the next few years.

MINERALIZED TISSUE DEFECTS

Tissue engineering is already being applied to the repair of periodontal defects, with the use of BMPs and research is

focused on applying tissue engineering principles to dental and craniofacial structures, probably because of the ease of access to these sites and the extent and nature of the clinical problems. Many problems managed by general dentists or specialists are prime candidates for tissue-engineering solutions, including fractures of bones and teeth, craniofacial skeletal defects, destruction of the pulp-dentin complex and periodontal disease (Lynch *et al*., 1999). BMPs and other growth-factor–rich preparations are being applied with a variety of natural and synthetic scaffolds. The latter are particularly important considerations for many dental and craniofacial applications. Not only are biologically appropriate scaffolds required for the cells and inductive factors, but the scaffolds should not adversely affect patient appearance. In that regard, an advantage may be gained from polymers that are allowed to flow into a defined site, rather than those that are fixed or implanted. Such polymers are currently being developed by a number of research groups (Peter *et al*., 1998; Bouhadir *et al*., 1999).

GENE THERAPY

There are several examples of using gene therapy and the most substantial body of work uses gene-transfer techniques as either primary or adjunctive therapies for head and neck cancers. Most of the focus has been on squamous-cell carcinoma and the cancer gene therapy effort is enormous. In the next decade, clinicians will likely be able to use gene-transfer technologies as part of their standard treatment of all neoplasias. Gene therapy also may offer a potentially novel approach to the treatment of severe chronic pain. Many studies have shown that genes can be readily transferred to cells in the central nervous system of animal models Finegold and colleagues recently showed that viral-mediated transfer of the ß-endorphin gene leads to effective analgesia in a rat pain model (Gleich *et al*., 1998; Wollenberg *et al*., 1999; Finegold *et al*., 1999).

ENGINEERING SALIVARY GLAND FUNCTION

Although most work in engineering new organ growth has focused on tissues whose loss or failure will lead to the patient's death (for example, the liver or endocrine pancreas), there are many circumstances involving tissue loss that are non–life-threatening, yet that markedly affect quality of life like the loss of salivary gland parenchyma and the ability to make saliva. For example, patients who receive ionizing radiation as part of their treatment for head and neck cancer experience irreversible salivary gland damage. In addition, patients with the autoimmune exocrinopathy Sjögren's syndrome also suffer the loss of salivary secretory tissue. Without saliva, these patients experience dysphagia, rampant caries, mucosal infections, dysgeusia and considerable oral discomfort (Wang *et al*., 1999).

The initial progress was achieved by using a natural substratum (denuded trachea) to the use of engineered polymer scaffolds. These efforts have focused on creating a rather simple device—a "blind-end" tube—suitable to engraft in the buccal mucosa of patients whose salivary parenchyma has been destroyed. The lumen of these tubes would be lined with compatible epithelial cells and be physiologically capable of unidirectional water movement. There is a realistic opportunity to develop a first-generation artificial salivary gland suitable for initial clinical testing relatively soon within about 10 years (Aframian, *et al.,* 2000; Baum *et al*., 1999).

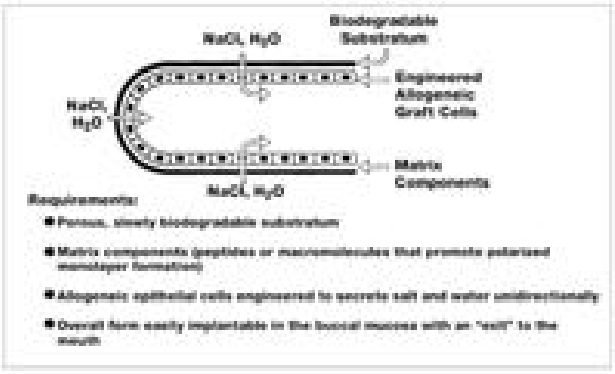

Figure 3. Schematic representation of a possible first-generation artificial salivary gland composed of a fluid-secreting blind-end tube

Cell-Based Therapy

Cell-based therapies are most commonly associated with bone marrow transplantation strategies. Bone marrow transplantation has been successfully used to treat a multitude of conditions, including genetic disorders, immune disorders, and tumors. More recently, interest has focused on marrow stromal cells as stem cells for tissues of mesenchymal origin. Hematopoietic stem cells in the bone marrow provide a continuous source of progenitors for blood cells but additionally contain cells that are stem cells for constractive tissue. Bone marrow stromal cells can differntiate in culture with osteoblasts, chondrocytes, adipocytes, or myoblasts and may also be a more *natural* source of biologic modifiers in the wound environment. These cells present an intriguing resource for their potential use in periodontal regeneration and are currently being explored on a basic scene level. Clinically, a significant challenge is the source of cells and the stringency of maintaining cells ex vivo before replacement in the statement site. The actual use of cell seeding in a periodontal application has been limited to a pilot report using PDL fibroblasts.

ETHICAL CONCERNS

There is significant debate among researchers in the biomedical community about at least two major ethical concerns related to tissue-engineered products. The first, tissue procurement, also is a manufacturing concern. For many tissue-engineered products (such as skin equivalents and bioartificial organs), viable cells are an essential component. Unless a patient's own cells can be amplified in an adequate and timely manner, enabling them to be used in the tissue-engineered device (that is, a cell autograft), then cells must be derived from another tissue.

This situation raises a number of significant ethical issues. For example, should the tissue source be other people or can an animal tissue (that is, a xenograft) be used? If the source is to be other people (that is, a cell allograft), should they be paid for their tissue samples (such as skin, liver)? This may induce people in financial distress to "donate" their tissues. Since fetal tissues often have more growth potential than adult tissues, should fetal tissues be used as a cell source? If, as with organs for transplantation, there are not enough cellular sources to meet the demand for any particular tissue-engineered device, how does one decide who will get the products (on the basis of need, ability to pay)?.

For several cell-based tissue-engineering products, the use of animal cells has been explored. Recently, researchers have called for a moratorium on research using cellular xenografts, in large part because of a hypothetical risk (Bach and Fineberg, 1998; Hunkeler, 1999). This risk is that an animal (in this case, porcine) virus might successfully overcome the human species barrier, perhaps mutate, and result in a serious human disease. Not surprisingly, there is no uniform agreement on this issue, although the dialogue has generally heightened awareness of ethical considerations in tissue engineering (Weiss, 1999).

THE IMPACT OF TISSUE ENGINEERING LIKELY WILL BE MOST SIGNIFICANT WITH MINERALIZED TISSUES, ALREADY THE FOCUS OF SUBSTANTIAL RESEARCH EFFORTS.

FUTURE PERSPECTIVES

Many advances have been made over the past decade in the reconstruction of complex periodontal and alveolar bone wounds. Developments in polymeric and ceramic scaffolding systems for cell, protein and gene delivery have undergone significant growth. The targeting of signaling molecules or growth factors (via proteins or genes) to the periodontium has lead to significant new knowledge generation using bioactive molecules that promote cell proliferation, differentiation, matrix biosynthesis, and angiogenesis. A major challenge that has been overlooked has been the modulation of the exuberant host response to microbial contamination that plagues the periodontal wound environment. For improvements in the outcomes in periodontal regenerative medicine, scientists will need to examine dual delivery of host modifiers or antiinfective agents to optimize the results of therapy. Further advancements in the field will continue to rely heavily on multidisciplinary approaches combining engineering, dentistry, medicine, and infectious disease specialists in repairing the complex periodontal wound environment. The advent of viable tissue engineering will have an effect on therapeutic options available to oral health specialists.

REFERENCES

Aframian, D.J., Cukierman, E., Nikolovski, J., Mooney, D.J., Yamada, K.Y. and Baum, B.J. 2000 Jun. The growth and morphological behavior of salivary epithelial cells on matrix protein coated biodegradable substrata. Tissue Engineering (in press), *Tisssue Eng.*, 6(3):209-16.

Alsberg, E., Hill, E., Mooney, D.J. 2001. Craniofacial tissue engineering. *Crit Rev in Oral Biol Med.*, 12(1):64-75.

Bach, F.H., Fineberg, H.V. 1998. Call for a moratorium on xenotransplants. *Nature.*, 391:326–8

Baum, B.J., Wang, S., Cukierman, E., *et al*. 1999. Re-engineering the functions of a terminally differentiated epithelial cell in vivo. *Ann. N. Y. Acad. Sci.*, 875: 294–300.

Bouhadir, K.H., Haussman, D. and Mooney, D.J. 1999. Synthesis and mechanical properties of cross-linked poly (aldehyde guluronate) hydrogels. *Polymer*, 40:3575–84.

Brittberg, M., Lindahl, A., Nilsson, A., Ohlsson, C., Isaksson, O., Peterson, L. 1994. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med.*, 331(14):889-95.

Finegold, A.A., Mannes, A.J. and Iadarola, M.J. 1999. A paracrine paradigm for in vivo gene therapy in the central nervous system: treatment of chronic pain. *Hum. Gene. Ther.*, 10:1251–7.

Giannobile, W.V. 1996. Periodontal tissue engineering by growth factors. *Bone.*, 19 (Suppl 1):23S–37S.

Gleich, L.L., Gluckman, J.L. and Armstrong, S. *et al*. 1998. Alloantigen gene therapy for squamous cell carcinoma of the head and neck: results of a phase-1 trial. *Arch. Otolaryngol Head. Neck Surg.*, 124:1097–104.

Hunkeler, D. 1999. Bioartificial organs: risks and requirements. *Ann. N. Y. Acad. Sci.*, 875:1–6

Krebsbach, P.H., Kuznetsov, S.A., Bianco, P., Gerhon Robey, P. 1999. Bone marrow stromal cells: characterization and clinical application. *Crit. Rev. in Oral. Biol. Med.*, 10(2):165-81.

Langer, R. 1993. J.P Vacanti Science, 260, p. 920

Lynch, S.E., Genco, R.J. and Marx, R.E. 1999. eds. Tissue engineering: applications in maxillofacial surgery and periodontics. Chicago: Quintessence Publishing.

Mooney, D.J., Powell, C., Piana, J. and Rutherford, R.B. 1996. Engineering dental pulp-like tissue in vitro. *Biotech Progress*, 12(6):865-8.

Nakashshima, M. 1990. The induction of reparative dentin in the amputated dental pulp of the dog by bone morphogenetic protein. *Arch Oral Biol.*, 35(7):493-7.

Naughton, G. 1999. The advanced tissue sciences story. *Sci Am.*, 280:84-5.

Nyman, S., Lindhe, J., Karring, T. *et al*. 1982. New attachment following surgical treatment of human periodontal disease. *J. Clin. Periodontol*, 9:290-6.

Parenteau, N. 1999. The organogenesis story. *Sci Am.*, 280:83-4.

Peter, S.J., Miller, S.T., Zhu, G., Yasko, A.W. and Mikos A.G. In vivo degradation of a poly(propylene fumarate)/b-tricalcium phosphate injectable composite scaffold. *J. Biomed. Mater. Res.*, 41:1–7.

Puelacher, W.C., Wisser, J., Vacanti, C.A., Ferraro, N.F., Jaramillo, D. and Vacanti, J.P. 1994. Temporomandibular joint disc replacement made by tissue-engineered growth of cartilage. *J. Oral. Maxillofac Surg.*, 52(11):1172-7.

Shalak, R. and Fox, C.F., 1988. Preface In: Tissue Engineering. R. Shalak and C. F. Fox, eds. Alan R. Liss, New York. pp. 26-29.

Sipe, J.D., Kelley, C.A. and McNichol, L.A. 2002. Reparative medicine: growing tissues and organs. *Ann. N. Y. Acad. Sci.*, 961:1–389

Slots, J., MacDonald, E.S. and Nowzari, H. 1999-2000. Infectious aspects of periodontal regeneration. *Periodontology*, 19:164–72.

Urist, M.R. 1965. Bone: formation by autoinduction. Science, 150(698):893-9.

Wang, S., Cukierman, E., Swain, W.D., Yamada, K.Y. and Baum B.J. 1999. Extracellular matrix protein induced changes in human salivary epithelial cell organization and proliferation on a model biological substratum. *Biomaterials*, 20:1043–9.

Weiss, R.A. 1999. Xenografts and retroviruses. *Science*, 285: 1221–2.

Wollenberg, B., Kastenbauer, M.H. and Schaumberg, J. *et al*. Gene therapy phase I trial for primary untreated head and neck squamous cell cancer (HNSCC) UICC stage II-IV with a single intertumoral injection of hIL-2 plasmids formulated in DOTMA/Chol. *Hum. Gene. Ther.*, 10:141–7.

****