Membranes for guided tissue and bone regeneration

Y Zhang*, X Zhang, B Shi, RJ Miron

Abstract

Introduction
Since the clinical use of dental membranes in the mid-1980s, guided bone regeneration procedures have become the standard in dental surgeries requiring space provision. A number of advancements have been made over the past 20 years in terms of their fabrication development. This review paper discusses original polytetrafluoroethylene non-resorbable membranes and the more recently employed innovative techniques to alter resorption periods in resorbable membranes. Furthermore, insight into future developments in membrane fabrication as well as platelet-rich fibrin membranes are discussed that will direct the next generation of guided bone regeneration.

Conclusion
There have been major advancements since the original expanded polytetrafluoroethylene membranes. Surgical procedures are no longer necessary as they cause discomfort to patients. Synthesis and natural biomaterials have been used in dentistry successfully for over 20 years, and their mechanical properties and degradation rates are being improved constantly. Furthermore, osteoconductive calcium phosphates and bioactive growth factors are now being incorporated to allow better bone formation.

Introduction

Principle of guided tissue and bone regeneration—its origin
It was not always believed that the periodontal ligament cells were responsible for the healing capabilities in the periodontium. From the 1970s until the mid-1980s, it was widely accepted and believed that the cells capable of regeneration of the periodontium were found in the alveolar bone. It was not until the late 1980s and conclusively at the beginning of the 1990s following a series of experiments in monkeys that conclusive evidence supported that progenitor cells in the periodontium were from the periodontal ligament tissue.

Based on these results, it was hypothesized that in order to optimize regeneration, if cells derived from the periodontal ligament and alveolar bone were exclusively allowed to repopulate the root surface away from the faster growing epithelium and gingival connective tissues, a higher regenerative potential would be observed; thus, the development of a “membrane-like” mechanical barrier was introduced. The development of “guided tissue regeneration” (GTR) was created in order to selectively guide tissue regeneration in the periodontium following periodontal disease. Following flap surgery in monkeys exposed to plaque for 6 months, a cellulose acetate laboratory filter or expanded polytetrafluoroethylene (ePTFE) was used to successfully prevent gingival connective tissue from contacting the root surface during healing and to produce a space for tissue ingrowth of the periodontal ligament. Following 3 months of healing, it was concluded by histological evaluation that the test membranes protested from epithelial down growth exhibited considerably more new attachment and bone regeneration. The results from this study confirmed the hypothesis that by selectively controlling the proliferation of the periodontal ligament cells and preventing contact from epithelium and connective tissues, the space-maintaining capability allowed for increased regeneration of the attachment apparatus of the tooth. Subsequently, Buser et al. introduced the basic principles of “guided bone regeneration” (GBR), that is providing the cells from bone tissues with a space intended for bone regeneration away from the surrounding connective tissue, by inserting barrier membranes to a bone defect. The work from the above-mentioned authors has been confirmed and reproduced in a number of animal and clinical studies increasing various periodontal defects including intrabony, furcation recessions and supra-alveolar defects.

Various approaches to increase new tissue and promote bone regeneration have been developed and compared (Table 1). The principles and limitations of each method suggest that GBR procedures are a better solution to non-membrane supported healing. This paper discusses the membranes used for guided tissue and bone regeneration.

Membranes for guided tissue and bone regeneration
The very first application of a membrane providing evidence that GTR could enhance regeneration of the human periodontium was a cellulose acetate laboratory filter by Milipore. Since then, a wide range of new membranes has been designed for various clinical scenarios, each

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possessing distinct advantages and disadvantages. As a medical application in dental implantology, barrier membranes should fulfill some fundamental requirements:

- **Biocompatibility**—the interaction between membranes and host tissue should not induce adverse effects;
- **Space-making**—the ability to maintain a space for cells from surrounding bone tissue to migrate for stable time duration;
- **Cell-occlusiveness**—prevention of fibrous tissue that delay bone formation from invading the defect site;
- **Mechanical strength**—proper physical properties to allow and protect the healing process, including protection of the underlying blood clot;
- **Degradability**—adequate degradation rate matching the regeneration rate of bone tissue to avoid a secondary surgical procedure to remove the membrane.

Several commercially available membranes, according to non-resorbable, synthetic resorbable and natural biodegradable materials, are classified in Table 2.

### Non-resorbable membranes

Non-resorbable membranes include expanded, high-density and Titanium-reinforced ePTFE (e-, d-PTFE and Ti-e-PTFE) and titanium mesh (Ti-mesh)\(^{13}\). Although a number of animal studies involving a variety of defect configurations and human histological data after treatment of intrabony lesions with ePTFE membranes demonstrate higher levels with clinical attachment level (CAL) gain and residual probing depths\(^{14}\), the requirement of a second surgical intervention to remove the barrier 4 to 6 weeks after implantation is a significant drawback\(^{12}\). The need for a second surgery may injure and/or compromise the obtained regenerated tissue, since it is known that flap elevation results in a certain amount of crestal resorption of the alveolar bone\(^{15}\). Furthermore, the use of non-resorbable membranes involves extra surgical times, which leads to increased costs and patient discomfort. These undesirable characteristics are often weighed with the positive effects of using non-resorbable membrane which include effective biocompatibility and ability to maintain sufficient space in the membrane for longer periods when compared to resorbable membranes. They have a more predictable profile during the healing process for their adequate mechanical strength, and they are easy to handle in clinics\(^{16}\).

### PTFE membrane

PTFE membranes were first introduced to dentistry in 1984; however, the membranes had been used clinically for some previous years as a vascular graft material for hernia repair\(^{17,18}\). Both sides of the porous structure of e-PTFE have their own features\(^{19}\): on one side, an open microstructure collar of 1 mm thick and 90% porosity retards the growth of the epithelium during the early wound healing phase; on the other side, a 0.15 mm thick and 30% porous membrane provides space for new bone growth and acts to prevent fibrous ingrowth. The average healing period after in vivo implantation is approximately 3–6 months (Table 2).

The advantages of d-PTFE, which feature 0.2 μm submicron pores on their membranes, is that they do not require primary closure and preserve the full width of keratinized mucosa\(^{20}\). Compared with the conventional e-PTFE, d-PTFE demonstrates

<table>
<thead>
<tr>
<th>Approaches</th>
<th>Principles</th>
<th>Typical examples</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Osteoconduction</td>
<td>The process in which the bone graft material acts as a scaffold for new bone formation on the native bone</td>
<td>Autogenous bone graft</td>
<td>Bone augmentation cannot achieve long-term stability and predictability without using barrier membrane</td>
</tr>
<tr>
<td>Distraction osteogenesis</td>
<td>Describes the spontaneous bone regeneration within an area created by gradual separation of two bone ends in a man-made fracture</td>
<td>Repair fracture in the jaw</td>
<td>Outcomes may be unpredictable and the man-made fracture would be risky</td>
</tr>
<tr>
<td>Osteoinduction</td>
<td>Recruit ideal factors such as mesenchymal stem cells, osteoprogenitor cells and growth factors to stimulate new bone growth</td>
<td>Bone morphogenetic proteins (BMPs)</td>
<td>Easy access to translating basic scientific research on induction of bone into reliable clinical applications</td>
</tr>
<tr>
<td>GBR</td>
<td>By barrier membranes to maintain sufficient space for the newly formed bone to fill in</td>
<td>Non-resorbable and resorbable membranes applied to implant surgery</td>
<td>Mechanical and chemical properties of membranes affects the final results</td>
</tr>
</tbody>
</table>

### Table 1 Different approaches to encourage bone regeneration

**Approaches**

- Osteoconduction
- Distraction osteogenesis
- Osteoinduction
- GBR

**Principles**

- The process in which the bone graft material acts as a scaffold for new bone formation on the native bone
- Describes the spontaneous bone regeneration within an area created by gradual separation of two bone ends in a man-made fracture
- Recruit ideal factors such as mesenchymal stem cells, osteoprogenitor cells and growth factors to stimulate new bone growth
- By barrier membranes to maintain sufficient space for the newly formed bone to fill in

**Typical examples**

- Autogenous bone graft
- Repair fracture in the jaw
- Bone morphogenetic proteins (BMPs)
- Non-resorbable and resorbable membranes applied to implant surgery

**Limitations**

- Bone augmentation cannot achieve long-term stability and predictability without using barrier membrane
- Outcomes may be unpredictable and the man-made fracture would be risky
- Easy access to translating basic scientific research on induction of bone into reliable clinical applications
- Mechanical and chemical properties of membranes affects the final results

**GBR**

- The creation of bone to fill in a secondary surgical procedure to remove the membrane.
- The requirement of a second surgery may injure and/or compromise the obtained regenerated tissue, since it is known that flap elevation results in a certain amount of crestal resorption of the alveolar bone.
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- The need for a second surgery may injure and/or compromise the obtained regenerated tissue, since it is known that flap elevation results in a certain amount of crestal resorption of the alveolar bone.

**Table 2**

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<table>
<thead>
<tr>
<th>Membranes</th>
<th>Commercial name</th>
<th>Manufacturer and nation</th>
<th>Material</th>
<th>Properties</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-resorbable membranes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e-PTFE</td>
<td>Gore-Tex</td>
<td>W. L. Gore &amp; Associates, Inc., USA</td>
<td>e-PTFE</td>
<td>Good space maintainer Easy to handle</td>
<td>Longest clinical experience</td>
<td>23,24</td>
</tr>
<tr>
<td></td>
<td>Gore-Tex-Ti</td>
<td>W. L. Gore &amp; Associates, Inc., USA</td>
<td>Ti-e-PTFE</td>
<td>Most stable space maintainer Filler material unnecessary</td>
<td>Titanium should not be exposed Commonly used in ridge augmentation</td>
<td>25</td>
</tr>
<tr>
<td>d-PTFE</td>
<td>High-density Gore-Tex</td>
<td>W. L. Gore &amp; Associates, Inc., USA</td>
<td>d-PTFE</td>
<td>0.2 μm pores</td>
<td>Avoid a secondary surgery</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Cytoplast</td>
<td>Osteogenics Biomedical., USA</td>
<td>d-PTFE</td>
<td>&lt;0.3 μm pores</td>
<td>Primary closure unnecessary</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>TefGen FD</td>
<td>Lifecore Biomedical., Inc., USA</td>
<td>d-PTFE</td>
<td>0.2–0.3 μm pores</td>
<td>Easy to detach</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Non-resorbable ACE</td>
<td>Surgical supply, Inc., USA</td>
<td>d-PTFE</td>
<td>&lt;0.2 μm pores 0.2 mm thick</td>
<td>Limited cell proliferation</td>
<td>29</td>
</tr>
<tr>
<td>Titanium mesh</td>
<td>Ti-Micromesh ACE</td>
<td>Surgical supply, Inc., USA</td>
<td>Ti</td>
<td>1,700 mm pores 0.1 mm thick</td>
<td>Ideal long term survival rate</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Tocksystem Mesh</td>
<td>Tocksystem, Italy</td>
<td>Ti</td>
<td>0.1–6.5 mm pore 0.1 mm thick</td>
<td>Minimal resorption and inflammation</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Frios BoneShields</td>
<td>Dentsply Friadent, Germany</td>
<td>Ti</td>
<td>0.03 mm pores 0.1 mm thick</td>
<td>Sufficient bone to regenerate</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>M-TAM</td>
<td></td>
<td>Ti</td>
<td>1,700 mm pores 0.1–0.3 mm thick</td>
<td>Excellent tissue compatibility</td>
<td>32</td>
</tr>
<tr>
<td>Synthetic resorbable membranes</td>
<td>OsseoQuest</td>
<td>W. L. Gore &amp; Associates, Inc., USA</td>
<td>Hydrolyzable polyester</td>
<td>Resorption: 16–24 weeks</td>
<td>Good tissue integration</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Biofix</td>
<td>Bioscience Oy, USA</td>
<td>Polyglycolic acid</td>
<td>Resorption: 24–48 weeks</td>
<td>Isolate the space from cells from soft tissue and bacteria</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Vicryl</td>
<td>Johnson &amp; Johnson, USA</td>
<td>Polyglactin 910 Polyglycolid/polyalactid 9:1</td>
<td>Resorption: 4–12 weeks</td>
<td>Well adaptable Resorption: 4–12 weeks Woven membrane Four prefabricated shapes</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Atrisorb</td>
<td>Tolmar, Inc., USA</td>
<td>Poly-DL-lactide and solvent</td>
<td>Resorption: 36–48 weeks</td>
<td>Interesting resorptive characteristics Custom fabricated membrane “Barrier Kit”</td>
<td>36</td>
</tr>
</tbody>
</table>

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All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.

All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.
obvious advantages as they prevent infections and easy operation for removal (Table 2).

**Titanium mesh**

Titanium-reinforced barrier membranes were introduced as an option for GBR, because they provide advanced mechanical support which allows a larger space for bone and tissue regrowth. The exceptional properties of rigidity, elasticity, stability and plasticity make Ti-mesh an ideal alternative for e-PTFE products as non-resorbable membranes. Rakhamia et al. demonstrated that there are four main advantages of Ti-mesh membranes over their alternative PTFE membranes: (1) rigidity provides extensive space maintenance and prevents contour collapse; (2) elasticity prevents mucosal compression; (3) its stability prevents graft displacement and...
(4) plasticity permits bending, contouring and adaptation to any unique bony defect. The main disadvantage of Ti-mesh membranes is increased exposure due to their stiffness and also a more complex secondary surgery to remove them.

Resorbable membranes
The advantage of resorbable membranes is that they permit a single-step procedure, thus alleviating patient discomfort and costs from a second procedure, avoiding the risk of additional morbidity and tissue damage. The main disadvantage of resorbable membranes is the unpredictable resorption time and the degree of degradation, which directly affects bone formation. The ideal membrane should be capable of being degraded or resorbed over time at the same rate that bone formation occurs. A list of studies describing resorption rates is given in Table 2.

Synthetic resorbable membranes
This series of resorbable membranes mainly consist of polymers [e.g., poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(ε-caprolactone) (PCL)] and their co-polymers. Collagen and aliphatic polyesters, such as polyglycolide or polylactide, are derived from a variety of origins and are fabricated with different approaches to become membranes for GBR (Table 2). Polyglycolide or polylactide can be made in large quantities, and the wide range of available materials allows for the creation of a wide spectrum of membranes with different physical, chemical and mechanical properties. Interestingly, the resorption of various membranes occurs via different pathways. In a review paper on this subject, Tatakis et al. describe that a large majority of collagen membranes is resorbed by enzymatic activity of infiltrating macrophages and polymorphonuclear leukocytes, while polymers are typically degraded through hydrolysis and the degradation products are metabolized through the citric acid cycle.

Membranes based on natural materials
The highest number of reported clinical studies involves the use of biodegradable resorbable membranes from natural materials (Table 2). Membranes based on natural materials are typically derived from human skin, bovine achilles tendon or porcine skin, and can be characterized by their excellent cell affinity and biocompatibility. The main drawbacks of these membranes are the potential of losing space maintenance ability in physiological conditions, high cost and possible danger of transmitting disease to humans when applying animal-derived collagen. Figure 1 demonstrates a scanning electron micrograph of a highly utilized natural membrane from bovine origin commonly used in GTR and GBR procedures (BioGuide, Geistlich Pharmaceuticals, Switzerland).

Focus on plasma-rich proteins (PRPs) as growth factors and membranes
PRPs isolated from platelets are a source of autologous growth factors that have been used for a variety of medical applications. The development of platelet concentrates was first described as early as 1970 through platelet concentrations—of platelet-rich fibrin (PRF). The PRF preparation protocol is very simple and inexpensive and is a great alternative to non-resorbable and resorbable membranes. Around 5 ml of whole venous blood is collected in sterile tubes and spun at 3,000 revolutions per minute for 10 min in a centrifuge tube. The blood is then settled into three layers: a red lower layer containing red blood cells, an upper clear coloured cellular plasma layer and the middle fraction containing the fibrin clot (Figure 2A). The middle layer can then be collected and shaped as desired and used as a PRF membrane (Figure 2B). This fibrin matrix can then be either used as a membrane in the wound-healing process has recognized several key components in blood that act to accelerate the healing of wounded tissues. Platelet-rich plasma was one of the first autologous modifications to fibrin glue that has been used with apparent clinical success in dentistry. This first generation of platelet concentrates contained approximately 95% platelets isolated through centrifugation. Although many growth factors are isolated via this method, the use of additional anticoaguants limits the natural healing process (Table 3).

More recently, a natural autologous membrane has been developed through platelet concentrations—that of platelet-rich fibrin (PRF). The advantages of this membrane are that they are entirely autologous and do not contain any anticoagulants or bovine thrombin such as PRP. The PRF preparation protocol is very simple and inexpensive and is a great alternative to non-resorbable and resorbable membranes. Around 5 ml of whole venous blood is collected in sterile tubes and spun at 3,000 revolutions per minute for 10 min in a centrifuge tube. The blood is then settled into three layers: a red lower layer containing red blood cells, an upper clear coloured cellular plasma layer and the middle fraction containing the fibrin clot (Figure 2A). The middle layer can then be collected and shaped as desired and used as a PRF membrane (Figure 2B). This fibrin matrix can then be either used as a membrane

Figure 1: Scanning electron microscopy of a porcine collagen membrane at magnifications of (a) 100× and (b) 400×, respectively.
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Table 3  Platelet protein classification and their biological role

<table>
<thead>
<tr>
<th>Classification</th>
<th>Protein</th>
<th>Biological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhesive proteins</td>
<td>von Willebrand factor (vWF) propeptide, fibrinogen, fibronectin, vitronec-</td>
<td>Cell contact interactions, homeostasis and clotting, and extracellular matrix compos-</td>
</tr>
<tr>
<td></td>
<td>ronec tin, thrombospondin 1 (TSP-1), laminin-8 (alpha4 and alpha5-laminin</td>
<td>ition</td>
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<tr>
<td></td>
<td>subunits), signal peptide-CUB-EGF domain containing protein 1 (SCUBE 1)</td>
<td></td>
</tr>
<tr>
<td>Clotting factors and associated proteins</td>
<td>Factor V/Va, Factor XI-like protein, multimerin, protein S, high-molecu-</td>
<td>Thrombin production and its regulation</td>
</tr>
<tr>
<td></td>
<td>lar-weight kiningoen, antithrombin III, tissue factor pathway inhibitor</td>
<td></td>
</tr>
<tr>
<td>Fibrinolytic factors and associated proteins</td>
<td>Plasminogen, plasminogen activator inhibitor-1 (PAI-1), urokinase</td>
<td>Plasmin production and vascular modeling</td>
</tr>
<tr>
<td></td>
<td>plasminogen activator (uPA), alpha2-antiplasmin, histidine-rich glyco-</td>
<td></td>
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<tr>
<td></td>
<td>protein, thrombin activatable fibrinolysis inhibitor (TAI), alpha2-</td>
<td></td>
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<tr>
<td></td>
<td>macroglobulin (2M)</td>
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<tr>
<td>Proteases and antiproteases</td>
<td>Tissue inhibitor of metalloprotease 1-4 (TIMPs 1-4), metalloprotein-</td>
<td>Angiogenesis, vascular modeling, regulation of coagulation and regulation of cellu-</td>
</tr>
<tr>
<td></td>
<td>ase-1, -2, -4, -9, A disintegrin and metalloproteinase with a thrombo-</td>
<td>lar behavior</td>
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<tr>
<td></td>
<td>sodin type 1 motif, member 13 (ADAMTS13), tumor necrosis factor-alpha-con</td>
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<td></td>
<td>verting enzyme (TACE), protease nexin-2, C1 inhibitor, serpin proteinase-</td>
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<tr>
<td></td>
<td>inhibitor 8, alpha1-antitrypsin</td>
<td></td>
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<tr>
<td>Growth factors</td>
<td>Platelet-derived growth factor, transforming growth factor beta1 and beta-</td>
<td>Chemotaxis, cell proliferation, cell differentiation and angiogenesis</td>
</tr>
<tr>
<td></td>
<td>2, epithelial growth factor, insulin-like growth factor type I, vascular</td>
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<tr>
<td></td>
<td>endothelial growth factor (A and C), basic fibroblastic growth factor</td>
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<td></td>
<td>(FGF-2), hepatocyte growth factor, Bone morphogenetic protein (BMP)-2,</td>
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<tr>
<td></td>
<td>4, -6, connecting tissue growth factor (CTGF)</td>
<td></td>
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<tr>
<td>Chemokines, cytokines and others</td>
<td>Regulated upon Activation—Normal T-cell Expressed, and Secreted (RANTES),</td>
<td>Regulation of angiogenesis, vascular modeling, cellular interactions and bone for-</td>
</tr>
<tr>
<td></td>
<td>interleukin-8 (IL-8), macrophage inflammatory protein-1 (MIP-1) alpha,</td>
<td>mation</td>
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<td></td>
<td>epithelial neutrophil-activating peptide 78 (ENA-78), monocyte chemo-</td>
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<td></td>
<td>tactic protein-3 (MCP-3), growth regulated oncogene-alpha (GRO-alpha),</td>
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<td>angiopoietin-1, IGF-1 binding protein 3 (IGF-BP3), interleukin-6 soluble</td>
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<td>platelet basic protein, neutrophil-activating protein-2 (NAP-2), con-</td>
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<td>nective tissue-activating peptide III, high-mobility group protein 1 (HM</td>
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<td></td>
<td>GGB1), Fas ligand (FasL), homologous to lymphotoxins, exhibits inducti-</td>
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<td></td>
<td>ble expression, and competes with herpes simplex virus (HSV) glycopro-</td>
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<td>tein D for herpes virus entry mediator, a receptor expressed by T lympho-</td>
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<td>cyttes (LIGHT), tumor necrosis factors (TNF)-related apoptosis-inducing l</td>
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<td></td>
<td>igand (TRAIL), stromal cell-derived factor-1 (SDF-1) alpha, endostatin-</td>
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<tr>
<td></td>
<td>l, osteonectin-1, bone sialoprotein</td>
<td></td>
</tr>
<tr>
<td>Antimicrobial proteins</td>
<td>Thrombocidins, defensins</td>
<td>Bactericidal and fungicidal properties</td>
</tr>
<tr>
<td>Others</td>
<td>Chondroitin 4-sulfate, albumin, immunoglobulins, disabled-2, semaphor-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>in 3A, prion protein (PrPC)</td>
<td></td>
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</tbody>
</table>

alone or combined with other bone grafts facilitating bone regrowth.56

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Current trends in the development of membranes

Many advancements and modifications have been made to membranes in order to improve the mechanical properties, degradation periods via cross-linking techniques and also bio-compatibility. Herein, we look at the...
Antibacterial properties

In recent years, the focus of many laboratories has been the design of membranes that have some form of antibacterial properties, which are utilized to prevent bacterial contamination and faster degradation rates of the membrane in contact with the epithelium and oral mucosa. Furthermore, surface modifications, and a combination with growth factors and bioactive molecules are also discussed.

Combination of membranes with growth factors

To date, various growth factors, cell-based approaches and use of bone grafting materials have been utilized for the treatment of the periodontium. One of the key factors influencing wound healing is the capability to recruit mesenchymal progenitor cells to the defect site. The local delivery of a wide variety of growth factors, such as platelet-derived growth factors (PDGF), and bone morphogenetic proteins that are both osteoinductive growth factors have been utilized in dentistry and possess the capability to further stimulate cell recruitment, proliferation and differentiation. Numerous in vitro, animal and clinical trials have demonstrated the advantages of these growth factors in combination with membranes.

Meanwhile, the clinical use of an enamel matrix derivative (EMD; Emdogain, Straumann AG, Basel, Switzerland) has been demonstrated to increase periodontal regeneration by increasing the formation of periodontal tissues including alveolar bone, cementum and the periodontal ligament. Accordingly, an in detailed set of in vitro experiments from members in our laboratory have demonstrated that EMD is able to drastically increase osteoblast and PDL cell proliferation and differentiation by up-regulating markers for osteoblast differentiation such as osteocalcin, bone sialoprotein, runx2 and collagen1. Furthermore, it is assumed that many of the regulatory cellular events are caused by cell condensations, which increase cell–cell contact molecules responsible for cell communication such as connexin43.

Conclusion

This paper reviews the basic principles in membranes utilized in GTR and GBR. Much advancement has been made since the original e-PTFE membranes, and surgical procedures are no longer necessary as they partially obstruct wound healing and increase patient discomfort. Synthesis and natural biomaterials have now been utilized in dentistry with great clinical success for over 20 years, and improvements are continuously being made regarding their mechanical properties and degradation rates. Furthermore, osteoconductive calcium phosphates and bioactive growth factors are now being incorporated to allow better bone formation, while antimicrobial substances aim to minimize the
influence of bacterial contamination. The next generation of membranes is expected to combine more functional biomolecules projected to increase the success of GBR therapy.

Acknowledgement
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30. Corinaldesi G, Pieri F, Sapigni L, Marchetti C. Evaluation of survival and success rates of dental implants placed at the time of or after alveolar ridge augmentation with an autogenous mandibular bone graft and titanium mesh: a 3- to 8-year
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