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Great progress has been made in the clinical applications of tissue engineering since the first edition of this book was published in 1999. Two pure, recombinant (synthetic) growth factors have received FDA approval for use in orofacial indications and are now available for widespread clinical use. Recombinant human platelet-derived growth factor (rhPDGF) was the first pure recombinant growth factor to be FDA approved for use in dentistry. It is indicated for promotion of bone and periodontal regeneration and treatment of gingival recession and has been widely used by clinicians in numerous indications since its commercial introduction. More recently, recombinant human bone morphogenetic protein 2 (rhBMP-2) also received FDA approval for sinus floor augmentation and alveolar ridge augmentation associated with extraction sockets. Both rhPDGF and rhBMP-2 were tested in lengthy and rigorous large-scale randomized controlled multicenter clinical trials and were FDA approved through a premarket approval (PMA) process, the most rigorous level of approval for medical devices.

The availability of rhPDGF and rhBMP for widespread clinical use ushers in a new era in patient care in periodontics and oral and maxillofacial surgery, allowing us to move from primarily passive, often highly invasive therapies to active ones that significantly stimulate the healing and regenerative processes. Traditionally, in most bone grafting and regenerative procedures clinicians have been faced with a choice of harvesting autograft or relying on osteoconductive matrices or cell-occlusive barriers. These techniques and materials served well when used in appropriate situations, with specific surgical techniques, and in relatively uncompromised patients. However, harvesting large amounts of autograft is time consuming and leads to increased pain and potential complications for patients, and passive therapies such as osteoconductive matrices and barrier membranes may only be used successfully in the treatment of a limited number of clinical problems.

The challenge and expectation for tissue engineering incorporating pure bioactive proteins, scaffolds, and eventually a source of regenerative cells is to achieve more predictable results in more diverse and compromised patient populations more quickly and with less pain. The genesis of this second edition was a belief by the editors and authors that we have indeed made tremendous progress in realizing these clinical goals and in achieving results that were previously only possible using highly invasive and time-consuming surgical techniques—or simply not possible at all on a predictable basis.

Time will tell how significant an impact these new therapies will have on clinical practice. As with all medical advances, it is likely that these early applications will result in some failures, as well as some successes, in indications that have yet to be contemplated. This process will lead to further refinements in combining matrices, pure bioactive protein therapeutics, and cells. It is the hope of the authors and editors of this book that the information presented here will be expanded as readers continue to learn and apply their knowledge to achieve the best outcomes for family, friends, neighbors, and all in need of our care.

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Clinicians may not have been aware that they were practicing tissue engineering but have indeed done so for many years. Tissue engineering is too often thought of as a sophisticated laboratory procedure in which cells, a tissue composite, or an organ is grown in tissue culture and then transplanted into a patient. Actually, tissue engineering may simply be directing or accelerating natural tissue healing by the clinician. Such tissue engineering may therefore be accomplished in vivo as well as in vitro. Examples of tissue engineering include many commonplace adjuncts in use today, such as hyperbaric oxygen, guided bone regeneration via the use of barrier membranes, demineralized bone matrix, enamel matrix derivative, and freeze-dried allogeneic bone. Although none of these involves all three elements of the tissue engineering triangle described in this chapter, they all either contain or direct one or more of these elements.

Recombinant human platelet-derived growth factor BB (rhPDGF-BB), recombinant human bone morphogenetic protein (rhBMP) on an absorbable collagen sponge (ACS), and platelet-rich plasma (PRP) actually contain all three elements of the tissue engineering triangle and thus are the most reliable techniques. This chapter will briefly explore the clinical applications of many of these methods, describing how they can be used effectively to enhance clinical outcomes as well as their limitations.

**Tissue Engineering Principles**

The basic principle of tissue engineering is a plagiarism of natural tissue regeneration and healing. That is, both require three elements that must be present and work together: cells, a signal, and a matrix. This concept is often represented as a triangle (Fig 4-1), indicating that an absence or dysfunction of one element will halt tissue regeneration.

**Cells**

The cells are thought to be pluripotential stem cells or cells that have only partially differentiated along their lineage. In bone regeneration, the cells range from CD34+ marrow cells or colony-forming unit (CFU) cells at their earliest stages all the way to the preosteoblast CBFA-1+ cells and even the endosteal or periosteal osteoblasts.
One unique histologic observation occurred with a specimen of a class II furcation regeneration where an enamel pearl was overlooked. A bridge of cementum developed over the pearl, an indication of the powerful regenerative capacity of rhPDGF-BB (Fig 5-17). Continued use of the signaling device (rhPDGF) has resulted in the treatment of severely compromised teeth with robust results.43

**Fig 5-17** New collagen fibers insert into the cementum-like material. Separation of new cementum-like material from enamel is likely an artifact. Mild inflammation is present. The morphology of the calcified tissue in the upper right corner gives the appearance of a second osteon or new cementum bridging the narrow gap between new cementum on the root surface and that covering the enamel pearl (toluidine blue–basic fuchsin stain; original magnification ×25).

**Fig 5-18a** Radiograph of a mandibular lateral incisor that has been deemed hopeless and referred for extraction and implant site development.

**Fig 5-18b** Clinical appearance of the lateral incisor. A wide interdental crater (arrow) is present on the mesial surface of the canine.

**Fig 5-18c** The defect has received an allograft, which has been hydrated and mixed with rhPDGF-BB. (Figs 5-18a to 5-18c from Nevins et al.77 Reprinted with permission.)

**Fig 5-18d** A collagen membrane has been placed for empirical reasons.
The interdental crater has not always responded to regeneration and frequently is treated with resection. However, in a case in which a mandibular incisor was referred for extraction, local bone development, and a potential implant, the patient agreed to allow treatment with rhPDGF-BB and an allograft substrate. This site also received a Bio-Gide membrane for empirical reasons. The probing depth was reduced from 13 to 3 mm and reopened after 11 months (Fig 5-18). Significant regeneration was apparent not only for the lateral incisor but also for the mesial interdental crater on the canine; this was substantiated radiographically (see Fig 5-18h).

A similar case treated with the same protocol involved severe bone loss associated with a mandibular lateral incisor and canine. The postsurgical result demonstrated excellent bone fill, evidence of a remarkable response to the combined treatment using rhPDGF-BB and allograft (Fig 5-19).

It is not reasonable to demand continuous histologic evidence of each case that is treated successfully. Once the proof of principle has been established, clinical and radiographic evidence is sufficient. The aforementioned regimens have significantly improved the prognosis of the treated teeth and accomplished the goal of allowing the