Editorial

From Passive to Active Regeneration: The New Gold Standard in Bone and Soft Tissue Grafting

I first began lecturing on tissue engineering and active vs passive healing in the early 1990s and published the tissue engineering triad for the first time in the dental literature in *Tissue Engineering: Applications in Maxillofacial Surgery and Periodontics* in 1999.[1] In 2006, Dr Wisner-Lynch and I wrote an editorial in this same journal, titled "From Passive to Active: Will Recombinant Growth Factor Therapeutics Revolutionize Regeneration?" Since then, it seems like most lectures I attend and many publications on dental tissue regeneration show or reference the tissue engineering triad in some form, and with good reason. It was a hypothesis in 1999, and today it is a clinical reality—and, I believe, the gold standard approach for achieving optimum clinical results. With the increasing use of growth and differentiation factors in dental surgery (not to mention orthopedics and spinal fusion surgery), use of simple passive conductive scaffold materials has progressed to today's gold standard: a combination of scaffolds with growth factors that actively promote tissue healing and regeneration.

While thousands, perhaps even tens of thousands, of studies have been conducted on a variety of growth and differentiation factors in dental applications, a majority of my research has focused on platelet-derived growth factor (PDGF). This is because the first few years of research showed that this molecule has the best opportunity, in my opinion, to improve patient outcomes in dentistry given its broad and potent ability to stimulate both bone and soft tissue healing. In 1989, my coworkers and I published the first report using PDGF to promote periodontal regeneration, and indeed the first report proving PDGF promotes bone growth in any part of the body, in the *Journal of Clinical Periodontology*.[2] That first report was a 2-week canine study that few thought would be successful. Today, pure recombinant (bioengineered) human PDGF-BB (rhPDGF-BB) has been proven in multiple FDA-audited, prospective, double- or triple-blinded randomized controlled clinical trials (RCTs) to be safe and effective in promoting soft tissue healing and bone regeneration in dental, dermal, and orthopedic indications. Indeed an RCT in 434 patients from 37 hospitals in the USA and Canada proved that rhPDGF-BB in combination with osteoconductive bone graft is as effective as autogenous bone from the iliac crest or proximal tibia in stimulating bone regeneration in the lower extremities.[3] In dental surgery, a prospective, triple-blinded RCT in 180 patients conducted by some of the best periodontists in the country in 11 clinical sites demonstrated that rhPDGF with an osteoconductive scaffold is superior to the osteoconductive scaffold alone.[4] Nearly 20 years later, this trial remarkably remains the largest prospective, blinded, FDA-audited RCT conducted on a regenerative product in dental applications, and it served as the basis for FDA approval of an rhPDGF-enhanced matrix (GEM 21S, Lynch Biologics) in periodontal regeneration.

As of 2020, over 500 papers on rhPDGF have been published in dental journals. A recent systematic review[5] of over 60 clinical studies demonstrated the consistency in outcomes of rhPDGF's ability to stimulate periodontal regeneration around teeth; further, extensive clinical evidence also showed rhPDGF's potential to improve clinical results in other parts of the oral cavity when used in combination with bone allografts or xenografts—such as improving extraction socket healing, sinus floor augmentation, and ridge augmentation—and in gingival recession defects when used with porous collagen matrices with or without underlying bone grafting materials.[5] This extensive review

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included results from over 1,250 patients and over 1,650 oral defects treated with rhPDGF. The peer-reviewed publications provide clear and compelling evidence that combining rhPDGF with bone allografts, xenografts, and/or autografts results in bone and periodontal regeneration in humans, with or without the use of membranes, and promotes true regeneration in root coverage cases; this differs from healing by scar formation and a long junctional epithelium that results from using connective tissue grafts.

I believe the body of evidence supporting the safety and effectiveness for rhPDGF-enhanced matrices has reached a level where active bone and soft tissue grafts are undoubtedly the gold standard for many indications. This observation is supported not only by the extensive scientific and clinical foundation demonstrating the therapeutic benefits of rhPDGF, but also the real-world use of rhPDGF to improve healing and bone regeneration in an estimated 5 million patients around the world, as of the time of this writing.

These extensive studies and clinical experiences support the conclusion that using rhPDGF in combination with a clinician's preferred bone graft (allograft, xenograft, autograft, or alloplastic materials) or with soft tissue grafting to treat gingival recession in many case types (not just severe ones) will improve a patient's postsurgical experience, reduce postsurgical complications, and improve clinical results.

While the 15-year track record of rhPDGF in dental surgery has been excellent, dentists should also take great pride in its impact on orthopedics and general wound healing. rhPDGF is the only growth factor whose wide clinical applications were discovered by a dentist and is now used broadly throughout medicine. No other regenerative biologic with therapeutic benefits discovered in dentistry has had such a broad impact in other applications in medicine.

Based on rigorous studies published in top-tier, peer-reviewed journals and on real-world evidence, it is clear that the answer to the question we posed here 15 years ago is "yes": active regeneration, grafts coupled with recombinant bioengineered growth factors, has indeed made regenerative outcomes possible today that simply were not possible previously, without needing to harvest autogenous tissues. What we did not predict many years ago was the large and significant impact on patient lives in other parts of medicine. So, I conclude this editorial with a new prediction: that we have not yet begun to realize the potential of tissue engineering and active healing throughout dentistry and medicine. We have only touched lightly upon the therapeutic benefits of incorporating stem cells with grafts and bioengineered growth factors into therapeutics. I believe that the discovery of how to safely and effectively incorporate cell therapy into our active bioengineered grafts will take regeneration to yet another level that we cannot now imagine. We shall see in another 15 years how true this prediction becomes. Until then, we should take advantage of recombinant bioengineered growth factor–enhanced grafts for the benefit of ourselves and our patients.

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