# Getting to the *Root* of dental implant tissue engineering

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## **Guest Editorial**

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Regenerative medicine and tissue engineering technologies have greatly benefitted medicine and dentistry over the past years (Zaky & Cancedda 2009). The use of protein-, gene- and stem cell-based therapeutics have been exploited significantly in the reconstruction of new tissues and organs (Discher et al. 2009). The field of oral and periodontal regenerative medicine has undergone significant recent advancements in areas such as total tooth engineering (Young et al. 2002) periodontal bioengineering (Seo et al. 2004) and oral implant osseointegration (Wikesjö et al. 2008). To date, a major "disconnect" exists between the principles of periodontal regeneration and oral implant osseointegration (see Fig. 1). That entity is the presence of a periodontal ligament (PDL) to allow for a more dynamic role beyond the functionally ankylosed or osseointegrated oral implant. In this month's issue of the journal, Gault et al. (2010) demonstrate for the first time in humans, the tissue engineering of PDL and cementum-like structures on oral implants to promote the formation of implant-ligament biological interfaces or ligaplants capable of true, functional loading. This work is elegantly displayed in both pre-clinical

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The author reports no conflict of interest. This work was supported by NIH/NIDCR DE 13397. and clinical experiments. Although the authors readily report that the findings are more of an early-stage, proof-of-concept, this work represents the potential that indeed tissue engineering approaches could become a reality in the formation of more *functional* implant fixtures in the future. The implementation of such an implant offers potential for titanium implant devices that can maintain form, function, and potential proprioceptive responses to allow for a tooth replacement more similar to a natural tooth (van Steenberghe 2000).

Gault and colleagues paper has extended the work two decades ago when Buser et al. (1990) demonstrated that the placement of dental implants in proximity to tooth roots allowed for the migration, population and maturation of cementoblastic cells that formed a cementum-like tissue with an intervening PDL that could be verified through polarized light microscopy. The mechanism of this phenomenon appeared to be due to the migration of cementoblast and PDL fibroblast precursor cells due to the contact or proximity of the toothrelated cell populations to the oral implant. Over the years, numerous investigators have attempted to develop such implants similar to the ligaplants as shown by Gault and colleagues, but with varying degrees of success (Choi 2000, Kim et al. 2009). Of interest in the Gault investigation is that PDL fibroblasts could be harvested from hopeless teeth from mature individuals, aged

35-55 years. These PDL fibroblasts revealed the stem cell responsiveness to adhere, proliferate and differentiate into cells capable of forming cementum, ligament and bone along the alveolus originally destroyed by periodontitis. This finding supports numerous reports demonstrating the regenerative potential of PDL stem cells to differentiate into committed progenitor cells capable of forming multiple tissues (Fleischmannova et al. 2010). Of interest, is that the investigators utilized bioreactors to culture primary cultures and maintain the "stem-ness" of these cells over a 3week in vitro culture period before transplantation to the osseous defects. The cellular seeding methodology allowed for a spatial distribution of cells over the surfaces of the prototype implant devices to eventually form the ligamentous constructs. There is indeed a growing body of evidence demonstrating the significant potential of the formation of ligamentous attachments to teeth or other biomaterials. These approaches use cell, protein and gene therapy as well as rapid material prototyping methods to guide ligament neogenesis (Ishikawa et al. 2009, Lin et al. 2009, Park et al. 2010). These structure-functional interfaces are crucial in the biomechanical loading of biomaterials with cells anchored to the surface to initiate activities such as adhesion, migration and subsequent polarization for fibrous attachment (Moffat et al. 2008, Petrie et al. 2009).





*Fig. 1.* Stem cell-based therapies in the bioengineering of teeth, periodontium and alveolar bone structures. In the situation of the formation of a tooth–implant interface, periodontal ligament stem cells offer the potential to form tooth–ligament–bone interfacial complexes.

This innovation offers many interesting possibilities if surgeons could utilize ready-made, off-the-shelf biological tooth replacements that could be delivered to serve as hybrid-material-living oral implants. These implants could potentially handle functional forces superior to traditional fixtures, possess proprioception and could be bodily moved via orthodontic ligaplant movements within alveolar bone. No longer would the installation of the fixture lead to an immovable titanium prosthesis unable to be shifted into more ideal positions. Would such an implant be better than existing osseointegrated tooth replacements? Currently, oral implants function very well with excellent long-term survival. Why add a ligament that may be more likely to undergo progressive bone loss? However, evidence has shown that bone loss is more rapid at the peri-implant interface for osseointegrated fixtures as compared with the tooth-bone interface (Lindhe et al. 2008). This advantage of the ligament might enhance such new implants to exhibit an improved survival? However, the implant success data shown by Gault and colleagues display

significant unpredictability in the human clinical situation. Further, a major concern at this time is the labour-intensive, impractical application of cell-based tissue engineering technologies. Cell therapy approaches are very robust in the ability to transplant-specific autologous cell populations to regenerate new, functional tissue. However, the use of autologous cells requires extensive regulatory requirements regarding cell procurement, confirmation of cell safety and ascertainment of contaminationfree cell populations before transplantation to the patient (Caunday et al. 2009). The costs and time required from a practical standpoint required for such tissue engineering applications is significant. However, let us appreciate and recognize this interesting advance as a first generation hybrid biomaterial that could be a prototype for future clinical approaches. It might be possible to generate such implant-ligament constructs using instructive biomaterials or signalling molecules to stimulate ligamentous tissue formation as non-cell therapy alternative technologies. In lieu of autologous tissues that carry with them corresponding regulatory burdens in individual patient assurances, many advancements in the use of allogeneic cells are also developing to propel the cell therapy field forward (Mansbridge 2009).

Thus, this proof-of-principle evidence represents an early hybrid approach of a biologically inspired material that exists as a dynamic, living construct. These types of living-synthetic hybrid biomaterials have tremendous potential in the treatment of multiple diseases including those affecting the oral, dental and craniofacial complex (Huebsch & Mooney 2009). Many unanswered questions remain with the ligaplant with regard to the long-term clinical findings and practicality of this approach to develop a hybrid synthetic-living tooth replacement, however, the concept opens up exciting possibilities for both periodontology and oral implantology.

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