J Clin Periodontol 2010; 37: 747–749 doi: 10.1111/j.1600-051X.2010.01589.x

Journal of Clinical Periodontology

Guest Editorial

Getting to the *Root* of dental implant tissue engineering

William V. Giannobile[1,2]

[1]Department of Periodontics and Oral Medicine, Michigan Centre for Oral Health Research, School of Dentistry, University of Michigan, Ann Arbor, MI, USA; [2]Department of Biomedical Engineering, College of Engineering, University of Michigan, Ann Arbor, MI, USA

Giannobile WV. Getting to the Root of dental implant tissue engineering. J Clin Peridontol 2010; 37: 747–749. doi: 10.1111/j.1600-051X.2010.01589.x.

Key words: oral/dental implants; periodontal ligament; regeneration; regenerative medicine; stem cells; tissue engineering

Accepted for publication 29 April 2010

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 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 tooth-related 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 3-week *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).

Conflict of interest and source of funding statement

The author reports no conflict of interest. This work was supported by NIH/NIDCR DE 13397.

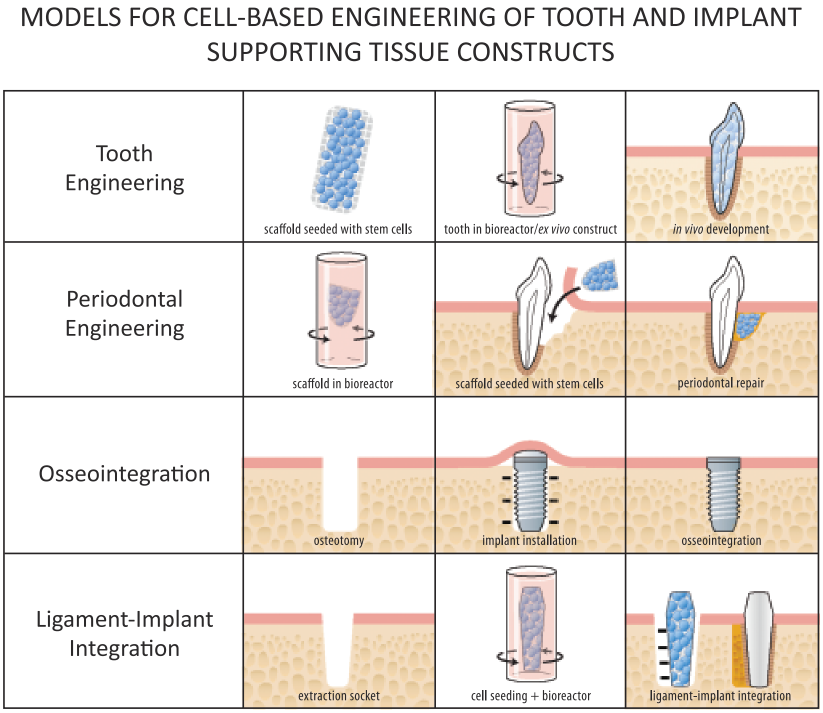

Fig. 1. Stem cell-based therapies in the bioengineering of teeth, periodontium and alveolar bone structures. In the situation of the formation of a tooth–implant interface, periodontal ligament stem cells offer the potential to form tooth–ligament–bone interfacial complexes.

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 contamination-free 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.

Acknowledgement

The author thanks Mr. Chris Jung for preparation of the figure.

References

Buser, D., Warrer, K., Karring, T. & Stich, H. (1990) Titanium implants with a true periodontal ligament: an alternative to osseointegrated implants? *International Journal Oral Maxillofacial Implants* **5**, 113–116.

Caunday, O., Bensoussan, D., Decot, V., Bordigoni, P. & Stoltz, J. F. (2009) Regulatory aspects of cellular therapy product in Europe: JACIE accreditation in a processing facility. *Biomedical Material Engineering* **19**, 373–379.

Choi, B. H. (2000) Periodontal ligament formation around titanium implants using cultured periodontal ligament cells. *International Journal Oral Maxillofacial Implants* **15**, 193–196.

Discher, D. E., Mooney, D. J. & Zandstra, P. W. (2009) Growth factors, matrices, and forces combine and control stem cells. *Science* **324**, 1673–1677.

Fleischmannova, J., Matalova, E., Sharpe, P. T., Misek, I. & Radlanski, R. J. (2010) Formation of the tooth–bone interface. *Journal of Dental Research* **89**, 108–115.

Gault, P., Black, A., Romette, J.-L., Fuente, F., Schroeder, K., Thillou, F., Brune, T., Berdal, A. & Wurtz, T. (2010) Tissue-engineered ligament: implant constructs for tooth replacement. *Journal of Clinical Periodontology* **37**, 750–758.

Huebsch, N. & Mooney, D. J. (2009) Inspiration and application in the evolution of biomaterials. *Nature* **462**, 426–432.

Ishikawa, I., Iwata, T., Washio, K., Okano, T., Nagasawa, T., Iwasaki, K. & Ando, T. (2009) Cell sheet engineering and other novel cell-based approaches to periodontal regeneration. *Periodontology 2000* **51**, 220–238.

Kim, S. H., Kim, K. H., Seo, B. M., Koo, K. T., Kim, T. I., Seol, Y. J., Ku, Y., Rhyu, I. C., Chung, C. P. & Lee, Y. M. (2009) Alveolar bone regeneration by transplantation of periodontal ligament stem cells and bone marrow stem cells in a canine peri-implant model. *Journal of Periodontology* **80**, 1815–1823.

Lin, N. H., Gronthos, S. & Bartold, P. M. (2009) Stem cells and future periodontal regeneration. *Periodontology 2000* **51**, 239–251.

Lindhe, J. & Meyle, J.Group D of European Workshop on Periodontology. (2008) Peri-implant diseases: consensus report of the sixth european workshop on periodontology. *Journal of Clinical Periodontology* **35** (8 Suppl.), 282–285.

Mansbridge, J. N. (2009) Tissue-engineered skin substitutes in regenerative medicine. *Current Opinion Biotechnology* **20**, 563–567.

Moffat, K. L., Sun, W. H., Pena, P. E., Chahine, N. O., Doty, S. B., Ateshian, G. A., Hung, C. T. & Lu, H. H. (2008) Characterization of the structure-function relationship at the ligament-to-bone interface. *Proceeding of the National Academy of Science USA* **105**, 7947–7952.

Park, C. H., Rios, H. F., Jin, Q., Bland, M. E., Flanagan, C. L., Hollister, S. J. & Giannobile, W. V. (2010) Biomimetic hybrid scaffolds for engineering human tooth–ligament interfaces. *Biomaterials* **31**, PMID 20471083.

Petrie, R. J., Doyle, A. D. & Yamada, K. M. (2009) Random versus directionally persistent cell migration. *Nature Review Molecular Cell Biology* **10**, 538–549.

Seo, B. M., Miura, M., Gronthos, S., Bartold, P. M., Batouli, S., Brahim, J., Young, M., Robey, P. G., Wang, C. Y. & Shi, S. (2004) Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet* **364**, 149–155.

van Steenberghe, D. (2000) From osseointegration to osseoperception. *Journal of Dental Research* **79**, 1833–1837.

Wikesjö, U. M. E., Huang, Y. H., Xiropaidis, A. V., Sorensen, R. G., Rohrer, M. D., Prasad, H. S., Wozney, J. M. & Hall, J. (2008) Bone formation at recombinant human bone morphogenetic protein-2-coated titanium implants in the posterior maxilla (Type IV bone) in non-human primates. *Journal of Clinical Periodontology* **35**, 992–1000.

Young, C. S., Terada, S., Vacanti, J. P., Honda, M., Bartlett, J. D. & Yelick, P. C. (2002) Tissue engineering of complex tooth structures on biodegradable polymer scaffolds. *Journal of Dental Research* **81**, 695–700.

Zaky, S. H. & Cancedda, R. (2009) Engineering craniofacial structures: facing the challenge. *Journal of Dental Research* **88**, 1077–1091.

Address:
William V. Giannobile
Department of Periodontics and Oral Medicine
Michigan Centre for Oral Health Research
School of Dentistry
University of Michigan
1011 N. University Ave.
Ann Arbor
MI 48109-1078
E-mail: wgiannob@umich.edu