

# Pulp Development, Repair, and Regeneration: Challenges of the Transition from Traditional Dentistry to Biologically Based Therapies

Gottfried Schmalz, DDS, DMD, PhD,\* and Anthony J. Smith, BSc, PhD†

### Abstract

The traditional concept of replacing diseased tooth/pulp tissues by inert materials (restoration) is being challenged by recent advances in pulp biology leading to regenerative strategies aiming at the generation of new vital tissue. New tissue formation in the pulp chamber can be observed after adequate infection control and the formation of a blood clot. However, differentiation of true odontoblasts is still more speculative, and the approach is largely limited to immature teeth with open apices. A more systematic approach may be provided by the adoption of the tissue engineering concepts of using matrices, suitable (stem) cells, and signaling molecules to direct tissue events. With these tools, pulp-like constructs have already been generated in experimental animals. However, a number of challenges still remain for clinical translation of pulp regeneration (eg, the cell source [resident vs nonresident stem cells, the latter associated with cell-free approaches], mechanisms of odontoblast differentiation, the pulp environment, the role of infection and inflammation, dentin pretreatment to release fossilized signaling molecules from dentin, and the provision of suitable matrices). Transition as a process, defined by moving from one form of “normal” to another, is based not only on the progress of science but also on achieving change to established treatment concepts in daily practice. However, it is clear that the significant recent achievements in pulp biology are providing an exciting platform from which clinical translation of dental pulp regeneration can advance. (*J Endod* 2014;40:52–55)

From the \*Department of Operative Dentistry and Periodontology, University Medical Centre Regensburg, Regensburg, Germany; and †Oral Biology, School of Dentistry, University of Birmingham, St Chads Queensway, Birmingham, United Kingdom.

This paper is based on a presentation from the International Association for Dental Research (IADR) Pulp Biology and Regeneration Group Satellite Meeting, which was held March 24–26, 2013 in San Francisco, California.

Address requests for reprints to Dr G. Schmalz, Department of Operative Dentistry and Periodontology, University Medical Centre Regensburg, Franz-Josef-Strauss-Allee 11, 93042 Regensburg, Germany. E-mail address: [gottfried.schmalz@ukr.de](mailto:gottfried.schmalz@ukr.de) 0099-2399/\$ - see front matter

Copyright © 2014 American Association of Endodontists. <http://dx.doi.org/10.1016/j.joen.2014.01.018>

### Key Words

Pulp regeneration, pulp capping, scaffold, stem cells, tissue engineering

Traditional dentistry has now evolved to a stage in which under optimal conditions success rates of up to over 90% have been suggested for some procedures (eg, for dental implants) after 10 years (1). The development of new materials with enhanced properties, careful attention to factors that influence the technique sensitivity of some procedures, and a generally greater awareness of oral health issues among the population have all helped to contribute to these improvements in treatment outcomes. Nevertheless, we must recognize that more traditional approaches simply seek to restore the structural integrity, function, and esthetics of the tooth. A much greater emphasis on the biocompatibility of dental materials in recent years has provided confidence that treatment does not invoke major adverse cellular responses in the tooth/periodontium, but treatment approaches generally still do not promote biological vitality in the tissues (restorative concept). As a consequence, a restored tooth may be non-vital and thus at increased future risk because of the absence of physiological defense mechanisms and nerves for pain transmission as well as being unable to undergo further root development if still immature.

Regenerative medicine is showing tremendous potential for improved treatment outcomes in many areas and has been stimulated by the immense advances made in biology over the last 2 decades. Of course, dentistry has long been a pioneer of regenerative medicine with the use of agents, such as calcium hydroxide, to promote wound healing in pulp capping procedures (2, 3) although such approaches have been somewhat empirical because of a lack of mechanistic understanding of the actions of these agents. The application of biomolecules, such as bone morphogenic protein-7 (BMP-7), bone sialoprotein (BSP), and other molecules, and controlling bacterial invasion have also led to the generation of dentin-like tissue after pulp exposure and, in some cases, a homogeneous calcification of the pulp chamber (4, 5). However, significant recent advances in pulp biology are now helping to address the regeneration of vital tissue, and this offers great scope for endodontics. This article provides an introduction to this special issue of the *Journal of Endodontics*, which contains articles from many of the invited speakers at the recent symposium on Pulp Regeneration: Translational Opportunities held in San Francisco, CA, during 24–26 March 2013.

### Pulp Biology and Endodontics

Endodontics is currently going through one of the most exciting periods of advancement in knowledge within the history of the discipline, especially in terms of the future clinical translation of scientific knowledge, largely driven by the recent advances in pulp biology. Key points are the characterization of stem cell populations in dental pulp and the recruitment of these cells to the tissue after injury, identification of bioactive molecules with potent cell signaling properties in the extracellular matrices of dentin and pulp, and elaboration of inflammatory events at the molecular level, among many other exciting advances. These are positioning clinical endodontics well to exploit a robust scientific understanding of post-injury and regenerative events to achieve novel biological approaches to tissue restoration and maintenance of tissue vitality in the clinic. As progress toward this goal rapidly evolves, there is still a need to focus on a number of key

questions that will enable new therapeutic strategies to have optimal outcomes and most effectively exploit a scientific basis to treatment.

Regeneration seeks to restore the physiological structure and function, and, therefore, it is important to recognize that understanding normal tissue development is fundamental to providing the blueprint for regenerative strategies. Such knowledge will also underpin novel tissue engineering approaches to restoring tissue function and vitality although progress toward these goals might also be facilitated through the development of therapies that seek to emulate more traditional clinical treatment protocols, such as root canal therapy, leading to more effective repair of the tissue albeit with less physiological outcomes.

## Repair and Regeneration in Endodontics

Several clinical strategies to promote repair and regeneration in the dentin-pulp complex are now emerging, which provide a valuable foundation on which future therapeutic approaches can develop. Although homogenous mineralization of the pulp chamber might appear to be a logical progression from current endodontic root fillings, the clinical merit and feasibility of such an approach remain to be shown. Some of the strategies proposed a focus on the suppression of infection and inflammation together with promoting tissue events encouraging vitality, especially revascularization. The introduction of revascularization procedures (6) has typically depended on blood clot formation to create a scaffold on which regeneration can occur, much in the same way as during any natural wound healing event in the body. Typically, this has been adopted in immature teeth with open apices in which cellular responses are likely to be optimal and can lead to root growth and apical closure although the “regenerated” pulp tissue may not always closely resemble its physiological counterpart. The use of triantibiotic paste and effective restorative materials for sealing the root canal in these revascularization procedures reflects the concomitant aims to suppress infectious/inflammatory events. The latter aims also underpin some of the protocols used in recent case series reports of “regenerative endodontics” (7, 8), which generally attempt to diminish the influence of necrotic tissue and post-injury inflammatory responses to provide a conducive environment for wound healing and tissue regeneration. The results of these protocols appear encouraging clinically although the histologic appearance of the regenerated tissues, despite single case reports (9), remains elusive.

## Dentin-Pulp Tissue Engineering

These approaches to repair and regeneration depend on the basic principles of tissue engineering, namely the interaction of a scaffold/matrix with cells and signaling molecules, albeit in the guise of natural wound healing events. More focused tissue engineering approaches to pulp regeneration are now emerging at the laboratory level although clinical trials are still to be undertaken. The use of a tooth slice model in which a poly(L-lactic acid) scaffold seeded with stem cells from human exfoliated deciduous teeth (SHED) cells was applied to the pulp space allowed the regeneration of pulp tissue with physiological-like appearance (10). Interestingly, this study model exploited the acidic nature of the poly(L-lactic acid) scaffold to locally release bioactive signaling molecules from the dentin matrix of the tooth slice highlighting the potential importance of this endogenous “fossilized” reservoir of bioactive molecules in dentin, which may contribute to the signaling of wound healing events (11). Furthermore, the study also showed the multipotent nature of SHED cells and their ability to differentiate into both odontoblast-like and endothelial cells in the vital regenerated pulp tissue (10), emphasizing the importance of stem cell selection when seeking cells capable of giving rise to the diverse range of cell types present in pulp. A novel self-assembling peptide hydrogel in which growth factors

were incorporated has been used to encapsulate both SHED and dental pulp stem cells (DPSCs) and provides a promising candidate biomaterial for future use in regenerative endodontics (12). The transplantation of side population cells (isolated by flow cytometry) with angiogenic and neurogenic potential from pulp with stromal cell-derived factor 1 into root canals of dog teeth after the removal of mature pulp tissue resulted in pulp regeneration (13). Clearly, these various reports of pulp regeneration at the laboratory level using tissue engineering approaches offer exciting opportunities for the development of novel future clinical treatment procedures. Tissue engineering of whole “bioteeth” (14–19) represents an ambitious challenge and is probably a rather longer-term clinical goal although very significant progress has been made toward this in the last decade. This proof of principle for the concept of engineering functional whole “bioteeth” offers exciting potential for the future although the clinical translational challenges are appreciable.

The emergence of these various tissue engineering approaches to pulp regeneration and biotooth formation has depended strongly on a good understanding of the biological events associated with physiological tooth development to underpin the selection of scaffolds, cells, and signaling molecules that mimic those involved in tooth development. However, the events of tooth development are under very tight temporospatial regulatory control; the latter of which is not always easy to replicate. Furthermore, in a clinical post-injury situation, there will also be the influence of infection and inflammation as these processes are gradually brought under control before regeneration. As a result, we still face a number of challenges before some of these exciting approaches to pulp regeneration can achieve effective clinical translation. The various speakers in this symposium upon which this issue of the *Journal of Endodontics* is based have helped to summarize the “state-of-the-art” in this area and provide significant new information, which will progress the clinical translation of pulp regeneration and in time will allow regenerative endodontics to become an everyday reality. Nevertheless, there is merit in the identification of some of the biological challenges associated with achieving clinical translation of pulp regeneration.

## Biological Challenges Associated with Pulp Regeneration

Tooth development provides the “blueprint” for understanding how cells develop the specificity to form the dental tissues and the exquisite control mechanisms, which regulate these processes in such a reproducible manner. In terms of pulp regeneration, the following areas continue to provide significant challenges before clinical translation can be realized:

1. Identification of the ideal cell source(s)
2. The relative merits of cell-based versus cell-free regenerative approaches
3. Epigenetic signaling and achievement of cell competence for odontoblast differentiation
4. The influence of the pulp environment on cell phenotype
5. The molecular signaling of odontoblast differentiation and subsequent regulatory control of secretory activity
6. The interplay of inflammatory and regenerative processes
7. Development of easily applied, injectable matrices
8. Dentin pretreatment procedures to harness endogenous “fossilized” signaling molecules

## Stem Cell Populations

Several different dental pulp stem cell populations have now been reported in the literature including dental pulp stem cells, stem cells

Download English Version:

<https://daneshyari.com/en/article/3146838>

Download Persian Version:

<https://daneshyari.com/article/3146838>

[Daneshyari.com](https://daneshyari.com)