

## Tooth Regeneration...Any Time Soon?

Editorial

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**Abbreviations:** PDL: Periodontal Ligament; RCT: Root Canal Therapy.

In the era of Regenerative Medicine, where are we from regenerating teeth? Patients-especially the partially or completely edentulous-are curiously taken by all hopes and hypes; while dentists, mostly the established private practitioners, with excitement in the background, are taken by worries from losing their practice. Tooth regeneration: How soon? Where are we? And what are we still missing?

Since coined in the 1990s [1], the paradigm of engineering [back] our body tissues has attracted many scientists and researchers. Together with the advances in genetics and the mapping of the human genome [2], Tissue Engineering became the highlight of a new era in medicine where our lost or diseased body parts are hoped to be replaced by genuinely natural parts regarded as “self” by the body with no synthetic material involved and without rejection.

For two decades now, it has been a pretty steep learning curve. In the attempt to recapitulating or mimicking the natural process of healing, research came across to understand stem cells [3], their niches, locations, division and proliferation, migration, differentiation and apoptosis; extracellular matrices [4], their biological and mechanical signaling cues; together with the flourishing of the science of biomaterials that help scaffold the new tissue constructs [5]. Depending on our current understanding about the physiology and turnover dynamics of a certain tissue or organ - inversely proportional to its complexity - its regeneration would be by the corner if it has not made it already to the clinic. For instance, skin regeneration is currently into practice for treatment from burns [6]; and islets of Langerhans regeneration is offered for treatment of type I diabetes [7]. To a lesser extent, and still

under research attempts, more complex tissues such as muscle [8] or bones [9] are still paving their way to clinical application.

As a combination of several biologically and mechanically distinct tissues, the extremely complex organ of a tooth is far yet - knowledge wise rather than time wise - near the actual clinical application of offering to a patient a regrown tooth into an edentulous space. So far, with their own hopes and challenges, two strategies have been attempted for tooth regeneration: the regeneration of individual tissues and the recapitulation of tooth development [10, 11].

The regeneration of individual tooth tissues implies studying and applying the healing mechanism of a certain tooth tissue. For cementum, cementogenesis is being studied and the attempts to cover the root dentin by neo-cementum are promising [12]. The periodontal ligament (PDL) is being studied for its harboring of mesenchymal stem cells that can regenerate the PDL [13], cementum and bone. The dental pulp and dentin are regarded as one complex tissue or organ (like bone and marrow), and several strategies are currently attempting to “obturates” back a manipulated or debrided pulp spaces with newly vascularized and innervated pulp tissue [14, 15]. Obviously, the hardest challenge is regenerating the hardest and most precious tissue we have in our body: enamel. Having lost its secreting cells (ameloblasts) upon formation (amelogenesis), our tooth enamel is condemned to be non-vital and non-regenerating tissue. Regeneration of enamel-like tissue, mainly chemically, has been attempted [16]; while some less repeatable literature have claimed success the differentiation of mesenchymal cells into ameloblasts to lay down enamel [17].

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To regenerate a whole tissue, the challenges facing the strategy of individual tissue regeneration is the interfaces between the different tissues [9], i.e. the dentinoenamel, cementodentinal junctions, the PDL (hard-soft-hard interface with bridging Sharpey's fibers) and the junctional epithelium. During tooth development these interfaces between two or more tissues, biologically and mechanically distinct, come into existence as the tooth is developing occluso-apically, maturing and erupting; rather than fully developed tissues getting "glued" together into an interface. The process of tooth development and the development of its complex interfaces can be compared to the bottom-up 3D printing or construction of a building, where at each layer all the construction components (bricks, plumbing, electric, etc...) are laid down for each floor level rather than concluding the brick skeleton and then creating holes for plumbing and electric wiring. Similarly, and obviously, "sticking" together two regenerated tissues is far from recreating their original wondrous interface.

The other strategy of recapitulating tooth development is about mimicking its epithelial-mesenchymal interaction, i.e. starting the tooth complex as a seed (tooth bud) into the jaw bones to mature and erupt as an individual functional tooth. Despite the actual process intricacy dwarfing our understanding, the strategy works and is promising on the animal research level [18]; however, for clinical application, is still hurdled by the following three challenges: the mechanical factor, the bacteria-laden oral cavity and, most important of all, the crown morphology.

Among all the tissue in the body, the mineralized tissues - bones and particularly teeth are directly affected by the mechanical load. Bone resorbs with lack of loading forces (like in microgravity experiments) while proper use under physiologic load stimulates its turnover [19]. Alveolar bone in particular, together with the periodontium, resorbs with the lack of biting forces after tooth extraction. Since occlusal forces are an integrated part of the tooth and the craniofacial development in general, it is not yet completely understood how the occlusal load perceived by a developing tooth bud through an adult jaw bone will affect its development.

The second challenge facing the whole tooth development strategy is about the oral environment being a physiologic home for bacteria. It is experimented and is of global consensus that a sterile microenvironment during any body manipulation or surgery, is a prerequisite for the success of the procedure. Operating against a bacteria-laden environment such as in the oral cavity, especially with florae different from research animals and different among individuals [20], is of a particular challenge for research standardization especially when tissue regeneration comes into play.

The third and most interesting hurdle facing tooth bud implantation is directing the development toward a certain crown morphology [18]: a molar versus an incisor for instance. We have already made tremendous strides in understanding tooth morphogenesis genetic signaling [21]. For instance to name a few, at the late bud stage homeobox genes at the enamel knots are strategically expressed along the epithelium, designing the sulcal and cuspal patterns of the crown [22]; *OSR2* gene determines the buccolingual distribution of mammalian teeth in a single row across the jaw [23]; and some regulatory homeobox genes depress *RUNX* to keep the PDL part of the periodontium non mineralized while still surrounded by mineralized cementum and bone [24]. Yet, we are still to understand what makes a crown develop

as molar versus as incisor; how different are the genetic signaling in the anterior versus the posterior parts of the jaw bone; and, while implanting a tooth bud into an adult jaw bone, what would be the changes in signaling compared to the ones occurring within embryonic jaw bone during development. As 21<sup>st</sup> century dentists, researchers and patients, we wait in excitement and awe for how the answers of these questions will unfold.

In this editorial, I have jotted down, and hopefully clarified, the current status of the field. Seeking beyond conveying information or knowledge, and as a dentist researcher who knows how hard it is to regenerate a tooth, I would like to bring to the readers, dentists and patients, a single take-home plea: appreciate the priceless natural tooth structure. Please don't take lightly grabbing your monster high speed handpiece to shave down the hardest and most precious sound enamel tissue, supposed to stay as long as we live [25]. Acknowledging that the best replacement of a lost tooth structure is a tooth structure, please make sure the patients leaves your chair with better, and more durable, tooth structure than what they came with. To date, no artificial material can perform as well as and genuinely replace a sound tooth structure. Please understand and explain to your patient that a tooth is never the same after root canal therapy (RCT). Lingering around but dead (a zombie?!), an RCTed tooth, has statistically short "existing" span than a live one [26] even with - or sometimes because of post RCT full coverage. And finally, unless of absolute necessity for the patient's health, please scrap off extraction from your treatment planning options.

And by the way, dentists, don't freak out from losing your business: you will be the ones implanting the "3<sup>rd</sup> generation" teeth... eventually.

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