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Editorial

# Injectable Hydrogels in Dentistry: Advances and Promises

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## Editorial

Hydrogels are natural or synthetic polymers with high water-absorbing capacity that are widely investigated for vast applications in regenerative medicine [1]. In recent years, injectable hydrogels have emerged as a promising biomaterial for therapeutic delivery of cells and bioactive molecules for tissue regeneration in dentistry and medicine because of their tunable tissue-like properties, controllability of degradation and release behavior, adaptability in a clinical setting for minimally-invasive surgical procedures, and ability to conform to the three-dimensional (3-D) defect upon gelling [2].

Natural hydrogels are often used in regenerative applications, due to their innate biological characteristics and resemblance to the native extracellular matrix (ECM). Some of the natural polymers include collagen, fibrin, hyaluronic acid, gelatin, chitosan and alginate. On contrary, synthetic hydrogels have finely-tuned properties such as degradation and mechanics, and are highly-reproducible with little batch-to-batch variation. The most commonly used synthetic hydrogels for regenerative applications are based on poly (ethylene glycol) (PEG). Of note, these highly-hydrated networks can be held together *via* physical or chemical cross links, can be made biodegradable, and responsive to specific stimuli such as pH and temperature, and can be engineered to deliver therapeutic cells and bioactive factors in a sustained and controlled fashion.

In craniofacial and dental tissue engineering, a paradigm shift is taking place from using synthetic implants and tissue grafts to tissue engineering approach employing biomimetic biomaterial scaffolds, particularly injectable hydrogels integrated with cells and bioactive molecules to regenerate a myriad of tissues including cartilage, bone, nerves, blood vessels and soft tissues (*i.e.* muscle, subcutaneous fat and skin). Similarly, in regenerative endodontic, injectable hydrogels have demonstrated the feasibility of delivering dental pulp stem cells, supporting matrix (*e.g.* enamel derivative [3]) and growth factors (*e.g.* stromal-derived growth factor (SDF)-α1, fibroblast growth factor (FGF)-2, and bone morphogenetic protein (BMP)-7) to support formation of the dentin-pulp complex [4]. A recent advance in tissue engineering further demonstrated the potential of the 'homing' approach for craniofacial and dentin-pulp regeneration, using biomaterial scaffold and bioactive molecules to activate endogenous cell migration and tissue repair [5].

Recent advances in materials science have enabled fabrication of synthetic and natural hydrogels with independent tuning of chemical composition and physical properties including stiffness. For example, the hyaluronic acid-tyramine (HA-Tyr) hydrogels were formed through the oxidative coupling of tyramine moieties, which was catalysed by horseradish peroxides (HRP) and hydrogen peroxide ($H_2O_2$) [6]. The gelation rates and stiffness of the hydrogels can be independently tuned by varying the HRP and $H_2O_2$, respectively. In cartilage tissue engineering, it was observed that the tunable 3-D microenvironment of the HA-Tyr hydrogels modulated mesenchymal stem cell chondrogenesis, where cellular condensation and cartilage formation were enhanced in the lower cross-linked matrices [6].

To overcome the possible limitations of individual material, composite hydrogels and hybrid systems have gained popularity in recent years. In bone tissue engineering, composite hydrogels may be created by blending two different polymeric materials and/or incorporation with inorganic phases such as hydroxyapatite, calcium phosphate and bio glasses to confer improvement to mechanical properties as well as added functionality for bone regeneration. Among the composite hydrogels, thermo-responsive chitosan-glycero phosphate hydrogel composite possess beneficial anti-bacterial and osteo inductive properties, and flexibility in blending with other materials such as the collagen [7] and gelatin [8], making the composite hydrogels an attractive candidate for craniofacial bone tissue engineering. In adipose tissue engineering, composite and multifunctional hydrogels may be fabricated by incorporating the decellularized adipose matrix [9] into the hydrogels matrix to recreate the adipose-like environment for adipose tissue regeneration [10].

Supra molecular hydrogels are the *next-generation* materials to enter the biomedical arena [11]. These materials are 3-D entities built from cross linking agents which bond non-covalently (*via* hydrogen bonds, π-π stacking and Vander Waals interactions) to form hydrogels. The use of injectable supra molecular hydrogels for tissue engineering is promising owing to their ability to deliver therapeutics, including cells and bioactive molecules in a highly-sustained and controlled manner [12].

Apart from expanding hydrogels chemistries, emerging tools and techniques including photo patterning [13], electro spinning [14] and co-culture of multiple cell types [15] are also being developed and applied towards engineering of multi-scaled and multi-layered hydrogel systems for regenerative applications [16]. Notably, there




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have been new and cell-friendly efforts to improve the porosity of hydrogels to enhance cellular infiltration through incorporation of stimuli-responsive microspheres [17] and microfibers [18] that may be dissolved in a controlled manner by specific changes in pH, temperature or exposure to enzymes. Utilizing these techniques may aid in the spatially controlled organization of multiple cell types and bioactive molecules and facilitate the progress towards regeneration of craniofacial complex tissues within the oral and craniofacial region.

Looking into the future, the design of injectable hydrogels that can be injected into the defect site and support cell infiltration and tissue in growth will be greatly explored. Hydrogels may be decorated with specific ECM ligands to recreate the naïve tissue environment and deliver the bioactive molecules in specific fashion (simultaneous *vs*. sequential) to orchestrate both exogenous and endogenous cell responses towards tissue regeneration. With great promise provided by these hydrogels, the issues regarding safety, degradation and clearance should also be addressed. New material chemistries and cross linking methods would be developed to enhance the material biocompatibility, functionality as well as the mechanical properties. Fundamental studies of cell-materials interactions will aid in guiding the design and development of the *next-generation* hydrogel systems for tissue repair and regeneration. These advances in h0079drogel design and engineering will continue to grow and aid in our future design of customized hydrogel systems, and guide the development of future therapies in dentistry.

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