SciForschen
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ISSN 2470-3206

International Journal of Nanomedicine and Nanosurgery

Editorial Volume: 2.1 Open Access

# Hydrogel-Based Nanostructured 3D Scaffolds for Bone Tissue Regeneration: Properties and Tools

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**Received date:** 18 Dec 2015; **Accepted date:** 21 Dec 2015; **Published date:** 27 Dec 2015.

**Citation:** Brasinika D, Dragatogiannis D, Charitidis CA (2015) Hydrogel-Based Nanostructured 3D Scaffolds for Bone Tissue Regeneration: Properties and Tools. Int Nanomed Nanosurg 2(1): doi http://dx.doi.org/10.16966/2470-3206.e103

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Tissue engineering necessitates the development of optimized scaffolds that facilitate cell growth and tissue development and regeneration. Bone regeneration is a complex biological process, including the recruitment of osteoprogenitor cells in the injured tissue and the utilization of a porous scaffold along with growth factors to induce tissue formation.

An ideal scaffold should address multiple physicochemical and biological requirements (e.g. biocompatibility, osteoconductivity, osteoinductivity) and serve as a 3D porous matrix, with interconnected open porosity, for cellular growth, proliferation, differentiation and subsequent extra-cellular matrix (ECM) development.

Moreover, stable material-tissue interface together with adequate mechanical strength and controlled degradation rate must be achieved so as to to provide structural integrity, until the desired tissue is regenerated naturally [1]. Recently, nanoindentation techniques have gained significant attention in the area of soft biological tissues and are being rapidly adopted to investigate mechanical properties of scaffolds, mimicking soft tissues, and elucidate the effect of degradation process in a wet environment. Accuracy of measurements especially in wet conditions requires new methods and techniques since hydrogels possess time dependent poro-elastic or poro-viscoelastic behavior and liquid capillarity and proper surface detection add major challenges [2,3].

Nanostructured hydrogel-based scaffolds have been studied intensively in the field of tissue engineering, since they provide a highly water-swollen polymeric network, resembling structure complexity of natural connective soft tissues. Their 3D structure consists mainly of chemically or physically cross-linked hydrophilic polymers (natural or synthetic), whose ability to swell in aqueous medium lead to the entrapment of cells inside the scaffold and to high permeability of oxygen, nutrients and cellular metabolites [4].

Porosity of bone substitutes is prerequisite, in order to allow high density of seeded cells and to support neovascularization when being implanted in vivo. In addition, porous structure increases mechanical interlocking between the implanted scaffold and the surrounding natural tissue, providing enhanced mechanical stability at the critical interface [5]. The relationship between pore size and osteoblastic activity is not fully determined; however a porous network consisting of both macropores (pore size ≥ 50 μm) and micropores (pore size ≤ 10 μm) has been proved beneficial for new tissue in growth [6]. Furthermore, by varying pore parameters, the biodegradation rate of the scaffolds is affected, since higher porosity increases surface area per unit volume.

Hydrogel-based scaffolds with an inner porous network are currently being fabricated by a variety of methods, such as gas foaming, solvent casting and particulate leaching, thermally induced phase separation or freeze drying [7]. The drawbacks of these techniques arise mainly from the utilization of highly toxic organic solvents, the incomplete removal of residues from the polymeric structures and the lack of full control over the interconnectivity of the pores. Additionally, most of these methods fail in producing scaffolds with tailored pore size and shape. To overcome these restrictions, additive manufacturing approaches can be employed to design and fabricate 3D scaffolds with a specific complex architecture. One of the most promising technologies includes 3D printing and more specifically Direct Ink Writing of hydrogel scaffolds [8]. During this process a virtual 3D model of the scaffold is created from a computer tomography data set and, subsequently, the material is extruded from a syringe nozzle in a layer-by-layer way, enabling formation of a well-defined porous structure with precise controlled interconnectivity. Moreover, in bone tissue engineering, 3D printing appears as a versatile tool for the direct fabrication of personalized implants, by exploiting computer aided design (CAD) programs.

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