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ISSN 2470-3206

International Journal of Nanomedicine and Nanosurgery

Mini Review | Volume: 3.1 | Open Access

Pressure-assisted Direct Ink Writing: A promising approach for the fabrication of Personalised Biofunctional Scaffolds

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Received date: 17 Jan 2017; **Accepted date:** 24 Feb 2017; **Published date:** 28 Feb 2017.

Citation: Brasinika D, Gkartzou E, Koumoulos E, Charitidis CA (2017) Pressure-assisted Direct Ink Writing: A promising approach for the fabrication of Personalised Biofunctional Scaffolds. Int J Nanomed Nanosurg 3(1): doi http://dx.doi.org/10.16966/2470-3206.121

Pressure-assisted Direct Ink Writing (p-DIW) technologies have widely attracted the interest of many researchers for the fabrication of 3D printed personalised implants with improved biofunctionality and defined micro architecture in the field of regenerative medicine [1]. This Additive Manufacturing (AM) technique presents high versatility in the materials that can be employed as bio inks, including natural and synthetic biopolymers, hybrid hydro gels and nanostructured or nanocomposites materials. In this context, by introducing innovative bio inks, which have been synthesised through bio inspired approaches simulating the bio mineralization process, p-DIW can lead to complex hybrid scaffolds with bone-like nanostructure. Mimicking natural bone's composition and crystallinity, significantly improves the cytocompatibility of the final scaffolds, providing a suitable microenvironment for cell proliferation and differentiation, and thus leading to enhanced osteointegration of the implant [2]. These structures could serve as a 3D template to guide the regeneration process of tissues, while maintaining mechanical integrity until the tissue regenerates naturally.

P-DIW combined with computer-assisted design could be exploited to create 3D scaffolds with defined internal multi-scale porosity, through a fully automated process with accuracy and repeatability. The formation of a continuous porous network with bimodal pore size distribution (both in the micro- and macro scale) and high levels of interconnectivity, considerably promotes the mineralized tissue in growth and vascularization [3,4]. Small pores ensure bone oxygenation, angiogenesis and nutrient and waste diffusion, while the larger ones are important in cellular development, orientation and directionality of cellular in growth and consequently are responsible of the scaffold's bioactivity.

A substantial advantage of computer-assisted design is based on the capability to design personalised implants which conform to the physical and biomechanical requirements of the host bones [5]. The design process of these complex structures begins with the acquisition of Computer Tomography (CT) or Magnetic Resonance Imaging (MRI) 2D image datasets, which can be imported and processed in specialized software to create a surface-rendered 3D volumetric model of the area of the bone defect, in order to determine the anatomical and micro structural characteristics that will define the external shape and internal micro architecture of the implant, as well as the precise site of insertion. This multi-scale hierarchical microstructure can be further enhanced through topological optimisation of the scaffolds [6].

The (nano) mechanical behaviour of 3D printed scaffolds is of relevant interest in applications which require not only load-bearing capability, but also need for assessing the surface adhesion and time dependent deformation. Typically, nanoindentation studies are carried out spanning different penetration depth on bulk (pore-free) materials and on the walls of porous scaffolds [7]. Nanomechanical mapping investigations is a promising method and allows assessing small-scale integrity of the scaffold walls [8]. Additionally, a characteristic nano indentation adhesion test is comprised of pressing the tip into the patterned sample, followed by unloading it at a constant rate and finally obtaining a distinctive (and often abrupt) pull-off force representing the adhering surfaces. Adhesion is observed in a load-displacement curve as a region of negative load during unloading [9]. The principle of this experiment is to put into contact the diamond probe tip and the flat polymer substrate and determine the maximum pull-force necessary to separate both materials. Quantitative assessment of mechanical behaviour is now possible for materials that were previously unattainable [10], especially for biomaterials that are hierarchical in structure. A key feature in this method is the selection of appropriate (often prototypes or modified) tip geometries and testing protocols.

The aforementioned combinatorial methodology constitutes a promising holistic approach for the automated fabrication of fully cytocompatible 3D printed scaffolds, targeting at tissue regeneration and not a temporary replacement of the damaged bone. Additionally, such AM processes ensure material waste minimization [11] and the inherent biodegradability of the bio inks employed renders them an environmental friendly solution. This innovative type of treatment decreases the risk of possible clinical complications (e.g. inflammatory response and subsequent rejection of the implant), since the 3D printed implant is *in vitro* seeded with cells extracted from small biopsies from the host before implantation, and the overall surgical costs are also reduced. The standardization and certification of this process are expected to pave the way towards a scaled-up production of patient-specific scaffolds, offering a viable solution to the worldwide increasing demand of compatible donors and/or improved implants.

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