3D printed and microfibrillar nanostructured blue hydrogels for bio-interfaces with potential in tissue regeneration

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Extrusion 3D printing represents a versatile fabrication technology that uses inks to print three-dimensional (3D) scaffolds promising personalised tissue regeneration by controlling architecture and functionalities. Electrospinning generates microfibrillar structures presenting porosity through fibers entanglement, beneficial for bone, cartilage engineering, or skin regeneration [1].

Tissue loss, caused by infection, resective therapy, or trauma, represents a significant challenge both clinically and societally. Bone is a highly complex tissue and the fabrication of bone grafts to regenerate large bone defects remains challenging. Scaffolds for bone regeneration are often inspired by the bone extracellular matrix (bECM). Natural origin hydrogel matrices are typically combined with a mineral phase [1;2]. Sustainable and blue biomaterials hold the promise to successfully assist tissue regeneration. Blue biotechnology uses marine bioresources for food and drug discovery, called blue materials, they include biopolymers such as fish collagen & gelatin. Moreover, to resemble filamentous proteins from bECM, such formulations are electrospun while to mimic the porosity of trabecular bone they are 3D printed. Nanoadditives are often used to reinforce or mimic the nanocomposite nature of bone. Typically, the effect of individual nanospecies is dogmatically investigated as rheological additive for improved printability, for bulk mechanical features and for overall cell-interactions. Interesting nanomaterial-cell interactions are reported but insufficiently explored or understood.

For the next bone fillers, it is important to tackle the potential of locally nanostructured microfibrillar structures to stimulate osteoblast response. The overall goal of this study is to develop platforms for bone regeneration including for the subchondral compartment, by converging 3D printing and electrospinning technologies, biomimetic nanostructured hydrogels, and bioactivity to replicating the complexity, specificity and function of native tissue. ECM-mimetic hydrogels, composite platforms, coatings and 3D printing inks have been widely engineered to match tissue properties and promote enhanced regeneration. We recently reported that calcium carbonate and biosilica two blue biomaterials, significantly enhance osteogenic response when enriching gelatin 3D printed and fibrillar structures [1;2]. In this study, a blue gelatin obtained from fish skin, is chosen as organic matrix for the incorporation of nanostructured blue mineral phase and for double-nanostructuring. The highly porous trabecular bone, including for the subchondral compartment will be extrusion 3D printed using biopolymers incorporating bioactive nanofilers (calcium carbonate and biosilica), and silver nanoparticles ensure antimicrobial activity. We developed bECM-inspired formulations for both electrospinning and 3D printing and then explored the effect of the nanoadditive content on the physico-chemical properties of the scaffolds and on the cellular response. The study aimed to support tissue growth and osteogenic differentiation. The physicochemical and mechanical properties of the scaffolds and the potential of the nanocomposites to support osteogenesis has been examined, including advanced microstructural analysis.

1. E. Olăreţ, et al, *Biomaterials Advances,* 2024, **161** 213894.
2. F. Curti, et al., Marine Drugs, 2022, **20**, 670.