# Editorial for the research topic: Functionalisation at Nanoscale to Enhance Specific Biological Activities

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This Research Topic collects different contributions on nanotechnology-based strategies for controlling and fine tuning biomaterials' properties at the nanoscale. Such modification allow the production of 3D environments with improved cell compatibility and ultimately functional tissue repair. In this research topic, we also present new insights on nanoengineered drug delivery systems.

The first article of this Topic (Casanellas et al. 2018), introduces the recent advances in 3D nanoengineered biomaterials for musculoskeletal tissue regeneration, highlighting the different methodologies used to process those. The authors show that both conventional and non-conventional technologies to manufacture 3D scaffolds with a fine control of the nanoarchitectural and compositional template for improved tissue integration. Particularly nanofibers had high surface area, which is optimal for cell adhesion, allowing an interconnected porosity for assisting nutrients transfer and cellular waste. Nanofibrous scaffolds can be produced by conventional electrospinning technology that represent a versatile and largely used method to manufacture nanofibrous scaffolds. Within the non-conventional technologies, 3D printing permit to control the design and manufacturing of scaffolds with complex structures and intricate geometries that can mimic better the nano- and micro- architecture of the tissues. Furthermore, the addition of nanomaterials during or after bioprinting process can enhance the scaffold cytocompatibility, tune the physico-chemical and mechanical properties, and direct cellular behaviour. Thus, the direct nanoscale bioprinting represent a new interesting scenario for mimic better the nanofeatures and nanostructure of the musculoskeletal tissue.

Within the proposed nanoengineered biomaterials, the use of cellulose has arisen recently attention from the researchers, due to its tuneable physico-chemical, and mechanical properties, allowing as ideal candidate for scaffold manufacturing. As discussed by (Pelling and Hickey 2019), cellulose can be found abundantly in nature, produced very easily and, thus, cellulose-based materials establish a low-cost platform. Moreover, cellulose-based materials satisfy the key criteria for biomedical application: bioactivity, biomechanics and extreme biocompatibility. In their review, the authors provide an up-to-date summary of the field status of cellulose-based nanomaterials in the context of bottom-up strategies for tissue engineering (*e.g.*, skin and wound dressing, bone tissue, blood vessels, and neural applications). Then, Peeling and Hickey highlight the influence of the different nanostructures between bacterial and plant-based cellulose on the biological response of the cells. Thus, these materials have great potential to open the next standard biomaterials generation due to their versatility and diversity of biochemical and physical properties.

Continuing with the application of nanotechnologies, it is extensively accepted that nano-textures applied on construct surfaces can influence strongly some biomaterial characteristics, such as wettability, protein absorption and cellular and/or bacterial adhesion. The importance of the surface functionalisation was tackled by (Liverani et al. 2019), who demonstrated the feasibility of different nanofunctionalisation strategies to modify the surface of electrospun membranes obtained using non-toxic solvents. Their outcomes show suitable results for all the functionalised polycaprolactone (PCL)-based meshes, with respect to the bare PCL, with a better cell behaviour on the membranes functionalised with the surface entrapment (after hydrolysis) of fibronectin. This extracellular matrix protein is fundamental for the nanoscale ligand-integrin affinity, and it is largely used for the functionalisation of electrospun meshes as well as for coating cell culture plates in order to enhance cell adhesion and spreading, in products already available on the market.

In another approach, to nano-functionalisation with protein and peptides, Al-Azzawi et al propose the potential way of improved drug uptake by the design and synthesis of low generations lysine dendrons with further functionalisation with ApoE-derived peptide (AEP) ligand. This methodology intends to enhance cellular uptake and drug delivery targeting to the brain for treatment of neurodegenerative diseases (Al-Azzawi et al. 2019). The high density of the terminal functional groups of the dendrimers is one of the key characteristics, as it allows several attachment sites at the nanoscale for drugs or other biomolecules complexation. In their study, the dendrimers as nanoscale carriers show strong ability to be internalised by brain endothelia within a receptor-mediated transcytosis (RMT) approach. This type of internalisation represents the first step for carrying bioactive molecules into the brain and has an attractive potential for novel therapeutics for central nervous system.

Finally, a chemical surface treatment for titanium and its alloys was presented in (Ferraris et al. 2019), who produced and characterized a Ti-oxide layer. Such surface had a high density of hydroxyl group present in the form of a sponge like nanotexture. The treated titanium-based surfaces: (1) presented enhanced bioactivity in simulated body fluid solution, encouraging the precipitation of new apatite crystals, and (2) determined an increase of samples anti-adhesive properties; particularly, a substantial inhibition in terms of bacterial viability and metabolism is evidenced for two different bacterial strains, *S. Aureus* and *A. Actinomyectemcomitans*, without compromising the material cytocompatibility.

We hope the readers find in this Research Topic a useful collection of articles in the emerging field of nanoscale functionalisation and manufacturing of medical systems for tissue engineering and drug delivery applications.

**Conflict of Interest Statement**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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