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TITLE: NANO-REINFORCED HYDRO-FILLED 3D SCAFFOLD FOR NEURAL TISSUE ENGINEERING

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ABSTRACT

Traumatic brain injury (TBI) presents a serious challenge for modern medicine due to the poor regenerative capabilities of the brain, complex pathophysiology, and lack of effective treatment for TBI to date. Current approaches (pharmacological and non-pharmacological) are largely focused on preventing further damage and rehabilitation instead of facilitating regeneration and tissue repair. Although a decellularized brain tissue matrix would be the best choice for a neural tissue engineering scaffold, the limitation brain tissue resource is a great obstacle for the practical application of this type of scaffold (decellularized matrix). Tissue-engineered three-dimensional (3D) scaffolds have shown various degrees of experimental success in augmenting cell survival, unfortunately, these biomaterial scaffolds present with various limitations that lead to a lack of successful clinical translation. Hybrid composite scaffolds hold promise for addressing some of the deficiencies of previous biomaterials scaffolds for tissue engineering application. The objective of this work was to prepare a novel neuromimetic three dimensional (3D) 3-in-1 scaffold system in the form of a nano-reinforced hydro-filled cryogel scaffold for neural tissue application. The scaffold was fabricated via a stepwise process whereby electrospun nanofibers where embedded in a polymer solution and crosslinker, incubation at sub-zero temperature (-20°C) to produce a cryogel, followed by filling of the nano-reinforced cryogel with a hydrogel. Fourier-transform infrared spectroscopy confirmed the presence of and interaction between the composite polymer materials in the scaffold. The temperature related observations from DSC and TGA analysis revealed the scaffolds thermal profile to be influenced by the combination of its composites. The degradation temperature of the scaffold was well above the physiological temperature of 37°C, indicative of stability and mechanical strength at ambient and physiological temperatures for potential application as thermostable implants/delivery devices. The

hybrid scaffold presented with an interconnected porous structure. A low mass loss of 36.5% was observed after 28 days. This slow degradation is desired and supports the suitability for practical application as an implant in the highly hydrated brain tissue environment. Mechanical characterization using unconfined compression test, demonstrated the scaffold to be viscoelastic, possesses shape memory properties, and a low compression modulus 525Pa. Effect on cell viability and proliferation evaluated by MTT assay showed that the 3-in-1 scaffold was non-toxic to both PC12 and A172 cells and therefore holds promising potential to support neural cell survival. Histological analysis revealed that the novel 3-in-1 scaffold successfully filled the lesion site, maintained tissue-scaffold contact, remained intact with the interconnected pores and was progressively infiltrated with cells and native tissue material throughout the residence period in the brain. Based on the observed results, the synthesized 3-in-1 scaffold properties suggest it has the potential to serve as an integrative and supportive platform for neural tissue engineering application. A 3-in-1 neuromimetic scaffold system is presented herein for application as a novel acellular implant to aid in neural tissue regeneration. This system is unique in the sense that it captures the multi-scale, multi-porous (micro/meso/macro-porous), intricate properties of native ECM (a key component of neural regeneration) in its design. Therefore, the results herein are unique to the composition and architecture of the novel 3-in-1 scaffold design, and thus contribute to potentially furthering knowledge influencing neural tissue regeneration research in comparison to any other previously reported CNS scaffolds in literature.