

2-D Graphene and Derivatives-Based Scaffolds in Regenerative Medicine: Innovative Boosters Mimicking 3-D Cell Microenvironment

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Regenerative medicine represents a multi-disciplinary medical area of increasing interest due to the major progress in cell and organ transplantations, as well as advances in biomaterials science and bioengineering. In 1993, Langer and Vacanti proposed the combined use of stem cells (SCs), nanomaterials-based scaffolds, and inductive factors as the basis for regenerative medicine (RM) [1]. Since then, researchers have been able to fabricate increasingly complex tissue/organ constructs, some of them are even used in clinics today as standard treatment for a variety of conditions (e.g. bone reconstruction) [2].

Scaffolds are usually processed in order to produce 3-D structures, with proper shape, size, and physical properties, tailored to fulfill specific functions such as mimicking tissue architecture and physiological responses [3]. Therefore, requirements for key scaffold(s) design and development can be summarized as follows: (i) biocompatibility; (ii) controlled porosity and permeability; (iii) suitable mechanical and degradation kinetics properties comparable to the targeted tissue; (iv) support for cell attachment and proliferation by adding nano-topographies to the biomaterial surface.

Some of the major current issues in RM are often related to: (i) relative difficulty to detect and isolate SCs from a variety of embryonic, fetal, and adult tissues; (ii) relative uncontrolled speediness of SCs proliferation rates; (iii) relatively low maintenance of SCs pluripotency; (iv) relative limited capacity of getting most SCs differentiated/specialized in a very specific lineage when required.

To date, despite the intensive progress in human SC research, only a few attempts to use carbon nanotechnology/carbon allotropes in RM have been reported. Among the carbonaceous nanomaterials, graphene (G), a 2-D nanomaterial, represents one of the most exciting nanomaterials. In 2010, Geim and Novoselov received the Nobel price of physics for having [4,5]: (i) demonstrated that graphite (GP), a 3-D nanomaterial, is in fact a stack of multi-G sheets; (ii) isolated G in 2004 using their famous "Scotch tape" technique. During the last decade, the intensive discoveries of the G's extraordinary intrinsic physical-chemical properties (e.g. electronic, mechanical, optical,

thermal, chemically-tunable surface), and the ease to isolate G has boosted further research and development (e.g. development of G-derivatives including functionalized hybrid nanocomposites), notably for scaling up production of cost-effective and quality G sheets (single or multi-layers) via developed innovative procedures (e.g. new exfoliation methods, epitaxial growth) [6-8].

In light of recent developments, artificially synthesized graphene-based biomaterials/ carbon allotropes (i.e. 2-D G, graphene oxide (GO), carbon nanotubes (CNTs), 3-D G foams, fluorinated G, activated charcoal composite (AC)) have demonstrated feasibility in supporting/promoting stem cell attachment/adhesion, growth and differentiation [9,10]. However, although the cell viability *in vitro* is not affected, the potential nanocytotoxicity (i.e. nanocompatibility and consequences of uncontrolled nanobiodegradability) in a clinical setting using humans remains unknown. Eventually, the establishment and compliance of international regulatory industrial and healthcare guidelines before commercialization and translational medicine are requested.

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