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Toxicology of graphene-based nanomaterials☆

Gaurav Lalwani [a,b,*], Michael D'Agati [b], Amit Mahmud Khan [b], Balaji Sitharaman [a,b,**]

[a] Theragnostic Technologies Inc., Long Island High Technology Incubator Suite 123, Stony Brook, NY 11790, USA
[b] Department of Biomedical Engineering, Stony Brook University, Stony Brook, NY 11794-5281, USA

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ABSTRACT

Graphene based nanomaterials possess remarkable physiochemical properties suitable for diverse applications in electronics, telecommunications, energy and healthcare. The human and environmental exposure to graphene-based nanomaterials is increasing due to advancements in the synthesis, characterization and large-scale production of graphene and the subsequent development of graphene based biomedical and consumer products. A large number of *in vitro* and *in vivo* toxicological studies have evaluated the interactions of graphene-based nanomaterials with various living systems such as microbes, mammalian cells, and animal models. A significant number of studies have examined the short- and long-term *in vivo* toxicity and biodistribution of graphene synthesized by variety of methods and starting materials. A key focus of these examinations is to properly associate the biological responses with chemical and morphological properties of graphene. Several studies also report the environmental and genotoxicity response of pristine and functionalized graphene. This review summarizes these *in vitro* and *in vivo* studies and critically examines the methodologies used to perform these evaluations. Our overarching goal is to provide a comprehensive overview of the complex interplay of biological responses of graphene as a function of their physiochemical properties.

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* Correspondence to: G. Lalwani, Theragnostic Technologies Inc., Long Island High Technology Incubator Suite 123, Stony Brook, NY 11790, United States. Tel.: +1 631 512 3980.

** Correspondence to: B. Sitharaman, Department of Biomedical Engineering, Bioengineering Building Room 115, Stony Brook University, Stony Brook, NY 11794-5281, United States. Tel.: +1 631 632 1810.

E-mail addresses: gauravlalwani06@gmail.com (G. Lalwani), balaji.sitharaman@stonybrook.edu (B. Sitharaman).

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1. Introduction

Carbon nanomaterials such as fullerenes, carbon nanotubes and graphene are the most widely researched class of materials and hold immense potential to impact several scientific disciplines [1–3]. Their transformative potential has been recognized with multiple honors including the Kavli and Nobel Prize [4,5]. Owing to the distinct arrangement of sp^2 bonded carbon atoms, each carbon nanomaterial can exhibit significantly different physical, morphological and chemical properties.

Graphene, a two-dimensional (2D) sheet of carbon atoms packed in a honeycomb lattice is widely regarded as a basic building block of graphitic allotropes (Fig. 1) [6]. The theoretical existence of graphene was discussed over 55 years ago by Slonczewski and Weiss [7]. Landau, Peierls and Mermin reported that existence of atomically thin 2D crystals (such as graphene) was practically impossible due to thermodynamic instabilities, a theory that was supported by several independent experimental observations [8–11]. However, in 2004, Novoselov and Geim isolated single sheets of graphene by micromechanical cleavage of graphite or the "scotch-tape method" [12] and characterized their quantum electrodynamics [13,14]. Since then research on graphene has exploded. The number of research papers published on graphene has been increasing exponentially (Fig. 2) attracting scientists from all areas of science and technology towards the graphene "gold-rush". In 2013, the European Union announced the graphene flagship project — a $1.3 billion 10 year investment in graphene research and development to translate graphene-based technologies from academic labs to the marketplace [15]. The Korean Graphene Project, also announced in 2013, is a $44 million 5 year investment for graphene research [16]. In 2011, United Kingdom committed £50 million investment for graphene research [17]. Recently, in October 2015, Chinese company Huawei Technologies has announced a $1 billion 5 year investment towards the development of information and communication technologies focused on graphene [18].

Graphene has interesting optical, thermal, mechanical and electrical properties. The sp^2 hybridization of 2D graphene plane results in delocalized out of plane π bonds that provide an exceptionally high carrier mobility (~200,000 $cm^2\ V^{-1}\ s^{-1}$ for suspended graphene [19,20] and ~500,000 $cm^2\ V^{-1}\ s^{-1}$ for graphene-based field effect transistors) [21,22]. Graphene exhibits room temperature quantum hall effect for electrons and holes [13,23]. Graphene sheets also exhibit high surface area (2630 $m^2\ g^{-1}$) [21], thermal conductivity (~5000 $Wm\ K^{-1}$) [24], mechanical property (Young's modulus of ~1 TPa) [25] and optical transparency (single layer graphene absorbs ~2.3% of visible light) [26].

Graphene can be synthesized using various physical (such as mechanical cleavage ("scotch tape method") [27] or arc discharge [28]) and chemical methods (chemical vapor deposition [29], Hummer's method (chemical oxidation of graphite followed by mechanical exfoliation) [30] or longitudinal unzipping of carbon nanotubes [31]). Depending on the method of synthesis, graphene can exist in various morphologies such as sheets, platelets, ribbons, onions and quantum dots (Fig. 3). Pristine graphene is apolar and very hydrophobic. It needs to be oxidized to improve its dispersibility in aqueous media.

Oxidized graphene is typically synthesized via chemical oxidation. Depending on the synthesis or morphology of the graphene, oxidized graphene are referred by various terminologies. For example, oxidized

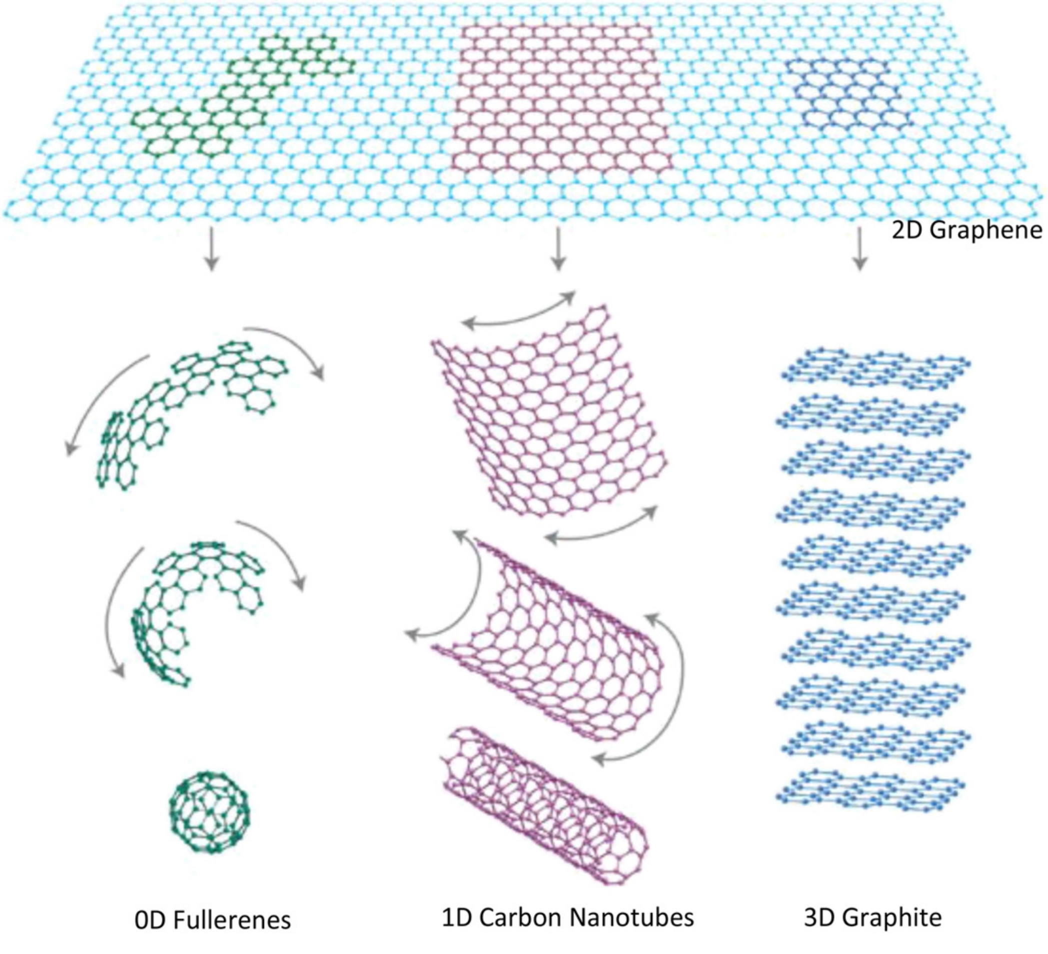

Fig. 1. Graphene is the building material for 0D fullerenes, 1D carbon nanotubes and 3D graphite.
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