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Prospects and Challenges of Graphene-Based Nanomaterials in Nanomedicine

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Introduction

Graphene is considered to be the 'wonder material' because of many unique and fascinating properties, such as high mechanical strength (200 times stronger than steel. Young's modulus ~ 1100 Gpa), exceptionally thin nanostructure (1 million times thinner than human hair and world's first two-dimensional material made up of single layer of hexagonally arranged sp^2-bonded carbon atoms, cf. (Figure 1), extraordinary electrical conductivity (mobility of charge carriers ~ 200,000 $cm^2 V^{-1} s^{-1}$), very high specific surface area (~ 2630 m^2/g), excellent thermal conductivity (~ 5000 W/m/K), highly stretchable, fully flexible yet impermeable, chemically inert, and intrinsically bio-compatible [1, 2]. Also the advent of simple, cost-effective and scalable fabrication techniques for single layer graphene made it one of the most attractive and sought after nonmaterial's in recent times [3], having applications in a wide range of fields including nanoelectronics, composite materials, energy technology, sensors, and catalysis, among others [4-6].

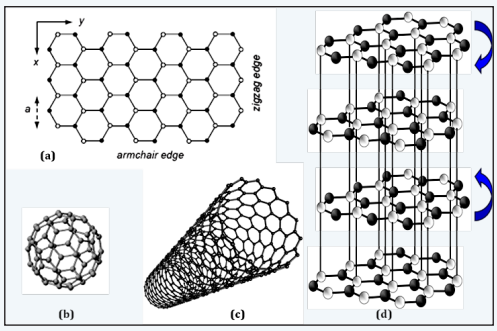

Figure 1: Schematic structures of (a) graphene layer (2D), which is (b) wrapped to form fullerene molecule (0D), (c) cylindrically rolled into carbon nanotubes (1D), and (d) stacked into graphite (3D) (Picture courtesy Wikipedia).

Additionally, the advent of the 'cousins' of graphene, such as graphene oxide (GO), reduced GO (rGO), graphane (hydrogenated graphene), graphone (semi-hydrogenated graphene), fluoro graphene (fluorine-terminated graphene), graphyne {benzene rings (sp^2) connected by acetylene (sp) bonds}, graphdiyne (graphene structure with two acetylene linkage) etc. cf. (Figure 2) [7-10] and the realization of their biological and chemical functionalization processes [11,12] made the graphene-based nonmaterial's highly attractive for biomedical applications. Indeed, after the pioneering work on the use of GO as an efficient carrier for drug delivery [11], a new horizon has been opened up to explore the use of graphene-based nonmaterial's for widespread biomedical applications. Although relatively new, but this research area becomes highly attractive and expanding rapidly with wide ranging applications, such as biological sensing and imaging, drug/gene delivery, antibacterial materials, biocompatible scaffold for cell culture, stem cell differentiation, mass spectrometry, etc. [12-20]. In fact, a recent study revealed that the biomedical applications of graphene and its derivatives supersede the non-medical applications. (Figure 3) depicts that the biomedical applications of the graphene and its derivatives are almost 63% as against 37% for the non-medical applications [21]. The broad bio-medical applications of the graphene and its derivatives in some major fields are pictorially presented in (Figure 4) [16].

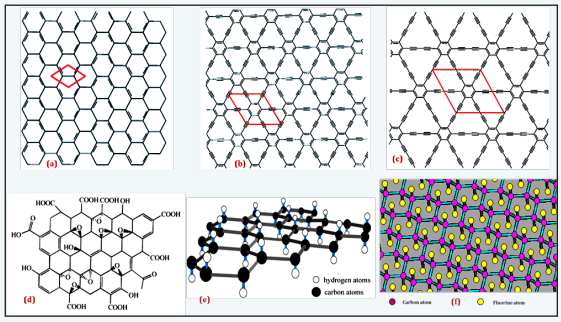

Figure 2: Schematic structures of (a) graphene, (b) Graphyne, (c) graphdiyne, (d) graphene oxide, (e) graphane, (f) fluoro graphene. The figure is adapted with permission from Inagaki M [9].

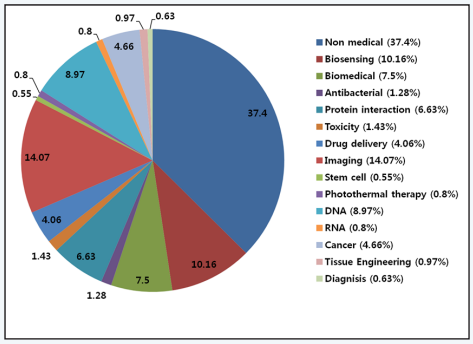

Figure 3: Comparative chart depicting biomedical applications of graphene and its derivatives against non-medical applications. The figure is adapted with permission from Mao et al. [21].

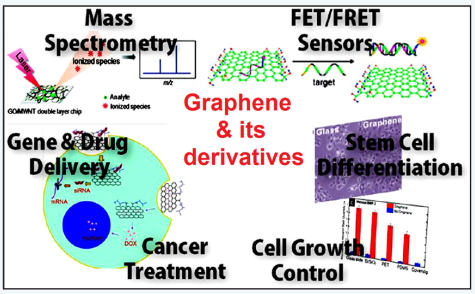

Figure 4: Some major fields of bio-medical applications of graphene and its derivatives. The figure is adapted with permission from Chung C et al. [16].

Graphene and its derivatives in bio-sensing and bio-imaging

As far as the graphene-based bio-sensors are concerned, the unique chemical, electrochemical, optical, electrical and electronic properties of graphene (and its derivatives) and the bio-functionalization of graphene-based nonmaterial's with various biomolecules and cells provide interesting applications in optical/electrochemical sensors, bio-imaging, electronic devices, mass spectroscopy etc. even without accounting for their improved biocompatibility, solubility and selectivity [22]. For example, a graphene-derivative/ oligonucleotide nanocomplex is used as a platform for DNA detection and analysis, in situ sensing of biomolecules, *in vivo* imaging of biomolecules in living cells, protein detection, sensing of heavy metals, pathogens etc. (Figure 5-i) schematically illustrates the mechanism of the interaction of fluorescent-tagged DNA with functionalized graphene, where both single-stranded (ss) DNA and double-stranded (ds) DNA are adsorbed onto a graphene surface (processes A and B, respectively). With ssDNA having stronger interaction against dsDNA, the fluorescence on the ssDNA darkens more, thus improving the bio-sensing capability. The adsorbed ssDNA can be detached from the graphene surface when a complimentary DNA nears the ssDNA (process C). Additionally, the adsorbed DNA onto the graphene is protected from being broken down by enzymes, thus improving the sensing efficiency [23]. Because of the aromatic character of the graphene (and its derivatives) and its ability to keep various ionic components onto its basal plane (which lead to the unique capacity to absorb bio-molecules), graphene nonmaterial's can become excellent bio-sensors in near future. Regarding the bio-imaging applications, a monohybrid of graphene-derivatives and fluorescent molecules is used as an in vitro and in vivo fluorescent cellular imaging probe. Graphene quantum dots' (GQD) photo luminescent properties have been explored for intracellular imaging without any surface processing or functionalization processes. Also a GO-magnetic nanoparticles composite is used for enhancing magnetic resonance imaging (MRI) signal for *in vivo* and non-invasive cellular imaging (Figure 5-ii). Additionally, radio-labelled GO (GO conjugated with some antibody) has been used for positron emission tomography (PET) imaging (a nuclear medical imaging) for cancer cells [24-28].

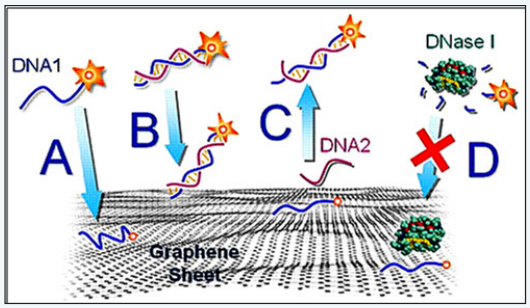

Figure 5: (i) Schematic illustration of the interaction of DNA with graphene for bio-sensing applications. The figure is adapted with permission from Tang et al. [23].

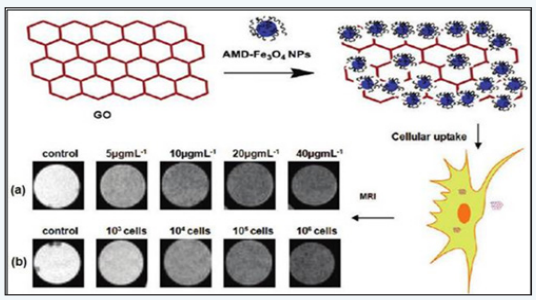

Figure 5: (ii)Schematic and pictorial representation of GO-magnetic nanoparticle composite for cellular magnetic resonance imaging (MRI). The figure is adapted with permission from Chen W et al. [27].

Regarding electrochemical sensing, a monohybrid consists of graphene / GO / reduced GO – metallic / organ metallic compound is used for electrochemical sensing of bio-macromolecules, enzymes and small molecules (like H_2O_2, β-Nicotinamide adenine dinucleotide {NAD+}, dopamine, glucose etc.). Apart from optical and electrochemical sensing and imaging, graphene-based field effect transistor (FET) (Figure 5-iii) becomes an attractive tool for electrical sensors for biomaterials and processes (like DNA hybridization, hormonal catecholamine molecules, protein-

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binding events, heavy metals etc.). Similarly, integration of graphene transistor arrays into a micro fluidic channel leads to the 'flow-catch-release' sensing of Malaria-infected red blood cells [29-33].

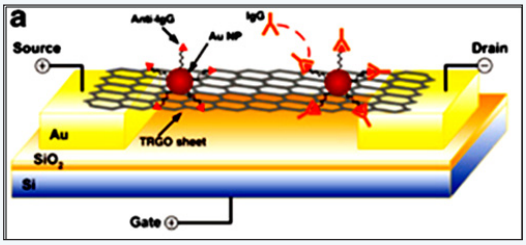

Figure 5: (iii) Schematics of graphene nanomaterials-based FET for electrical detection of protein binding events. The figure is adapted with permission from Mao et al. [33].

Also, interfacing graphene and its derivatives with micro/nanoscale biomaterials/components leads to the fabrication of some bio-electronic devices for detection of DNAs, proteins, and pH sensors etc. Also graphene-based nonmaterials are used as a novel matrix for mass spectrometry assay of biological molecules. The ultra-high specific surface area of graphene with double-sided aromatic scaffold provides extremely large loading capacity in surface-enhanced laser desorption-ionization (SELDI) probe for DNA detection and analysis [33-35].

Although majority of the above-mentioned graphene-based biomedical applications involve pristine graphene, GO and rGO, but some of the newly developed graphene derivatives are also reported to show interesting and novel applications in biomedicine. For example, graphdiyne showed promising amino acid detection capability and can potentially be used in bio-sensing applications [36]. Theoretical modeling depicted pristine graphene has excellent desalination properties [37]. Therefore, functionalized graphene can be used for cyanobacteria cultures to generate large biomass for bio-desalination process [38]. Graphane, the semi-hydrogenated graphene, has promising applications in organic ferroelectrics [39], thereby opening up promising opportunities in the field of molecular ferroelectricity, which has interesting links with biological ferroelectricity [40]. Graphane, the hydrogenated graphene, revealed improved bio-sensing properties over graphene and thus may be used in novel bio-sensing devices [41].

Challenges

The major challenges in the field of graphene and its derivatives for bio-sensing and bio-imaging applications are (i) identification of practical advantages over conventional bio-assay tools, (ii) reproducibly, and (iii) reliability. Although a large volume of studies have been published in this area of research in recent times, and in many cases the detection sensitivities are found be better than the conventional methods, yet, the batch-to-batch variations of the graphene-based nano-bio-sensors are far from satisfactory, and needs more attention [19].

Graphene and its derivatives as bio-delivery carriers and therapeutic applications

Some of the unique properties of graphene and its derivatives such as large surface area, chemical purity, easy bio-functionalization, availability of delocalized electrons for easy solubility and bondage of drug molecules, high drug loading capacity of the double-sided graphene sheet, its lipophilic nature to help cell membrane barrier penetration for in vivo drug delivery etc. made graphene nonmaterial's highly promising for bio-delivery carriers for Nanomedicine applications (Figure 6). After the seminal work on the *in vitro* loading and release of anti-cancer drugs by GO [11], a series of works have been published on in vitro controlled drug loading and targeted delivery of drugs via graphene and its derivatives as bio-delivery carriers for drug delivery and cancer therapy as well as other non-cancer treatments [13-21,42-53].

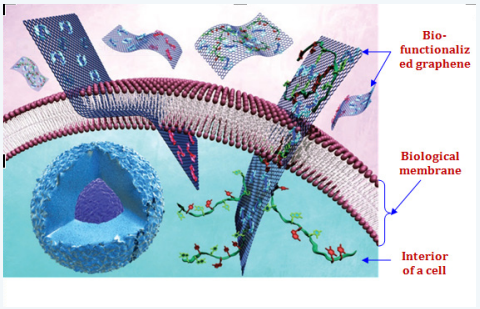

Figure 6: Schematic illustration of penetration of graphene inside a cell for drug delivery. The figure is adapted with *permission from Macmillan Publishers Ltd: Nature 490 (2012) 193-200 © 2012.*

Apart from the in vitro delivery of small drug molecules, graphene and its derivatives are reported to show the capability of *in vitro* gene transfection, which is very important to treat various diseases caused by genetic disorders, including cystic fibrosis, Parkinson's disease, and cancer. For example plasmid DNA (pDNA), silencing RNA (siRNA) etc. are loaded in graphane derivatives for intracellular transfection into cancer cells with improved cell killing efficacy [54-58]. As lack of efficient and safe gene vectors pose a major challenge in the development of gene therapy [59], use of graphene and its derivatives in the field of gene delivery can open up new possibilities to treat genetic disorders.

Other important in vitro therapeutic applications of graphane nanomaterials are the phototherapy, such as photo thermal (PTT) and photodynamic (PDT) therapy, which are used to control disease by specific light irradiation. The advantage of phototherapy is that, graphene nano-agents can specifically target and kill cancer cells which are exposed to the light, without significantly damaging the normal organs in dark, thus exhibiting remarkable advantages in terms of enhancing the cancer killing specificity and reducing the side effects [60]. In PTT, because of strong optical adsorption in the near-infrared (NIR) region of graphene, graphene-based nonmaterial's are targeted to the

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cancer cells followed by NIR radiation to generate sufficient heat for cancer cell killing (Figure 7-i,ii). On the other hand, in PDT, graphene-based nanomaterials are irradiated with a suitable wavelength of light to generate reactive oxygen species (or free radicals), which irreversibly damage/kill the cancer cells. For enhancement of therapeutic efficacy, combinatorial therapy like PTT and chemotherapy has been used. In some cases, a combination of PTT and PDT showed much improved cell killing efficacy via improved delivery of photo sensitizers through PTT effect of graphene, followed by generation of cytotoxic singlet oxygen through PDT effect of functionalized graphene derivatives. Some groups reported high therapeutic efficacy with graphene-photo catalyst nanohybrid via combinatorial PTT and photo catalytic therapy [11,61-73].

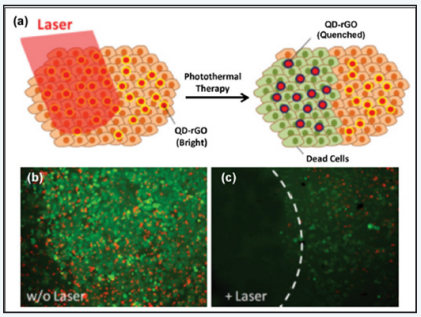

Figure 7: (i) Schematic illustration of photo thermal therapy. (a) Reduced GO (rGO) quantum dots (QDs) are irradiated to kill cancer cells. Fluorescence images of cells before (b) and after (c) irradiation. The figure is adapted with permission from Hu SH, et al [64].

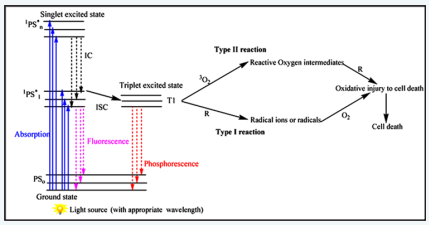

Figure 7: (ii) Modified Jablonski diagram depicting the process of photodynamic therapy. When PSs in cells are exposed to specific wavelengths of light, they are transformed from the singlet ground state (S_0) to an excited singlet state (S_1–S_n), which is followed by intersystem crossing to an excited triplet state (T_1). This can follow two separate pathways. Type I reaction occurs when the excited molecule reacts with organic substrates (R) and produce radical ions or radicals. Type II reaction takes place when the energy is transferred from the excited photo sensitizer to molecular Oxygen ($^3O_2$) to form reactive oxygen intermediates. These intermediates react rapidly with their surroundings including cell wall, cell membrane, peptides, and nucleic acids.

Abbreviation: IC: Internal Conversion; ISC: Intersystem Crossing; PS: Photo Sensitizer; ^{1}PS*: Singlet excited photo sensitizer.

The figure is adapted from Debel TA et al. [66] © 2015 MDPI AG [The figure is from an open access article distributed under the Creative Commons Attribution License (CC BY) which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited].

Although considerable progress has been made on the exploration of graphene and its derivatives as delivery carriers and therapeutic applications *in vitro*, but *in vivo* test needs considerable attention for real time treatments of clinical cancer and other diseases. Only a handful of reports are published in this direction. The first report in this regard presented the intravenous administration of bio-functionalized graphene derivatives (labeled with a NIR fluorescence dye but not carrying any drug) for passive tumor targeting in mouse xenograft models and killing the cancer cells via PTT [74]. Thereafter, few reports have been published on the in vivo test of graphene nonmaterials as delivery carries and therapeutic applications via PTT and PDT. The effect of size and surface chemistry of graphene derivatives on the in vivo photo thermal cancer treatment have also been studied [63-65,72,75-79].

Challenges

The major challenges for the applications of graphene-based nonmaterial's in drug/gene delivery and therapy are the realization of (i) sufficiently high drug loading capability for practical uses, (ii) suitable *in vivo* drug distribution and release profiles, (iii) proper chemical modifications of graphene derivatives for cell membrane barrier penetration for drug delivery into the interior of a cell, (iv) understanding of *in vitro* and *in vivo* toxicity profile, bio-distribution, bio-compatibility and bio-degradability of graphene and its derivatives. Several groups already started exploring the long term and short term cytotoxicity effects of graphene-based nonmaterial's in vitro [11,46,80-83] and in vivo [24,74,76,82,84-88]. Yet this field is very much open as the toxic effects of graphene is highly dependent on its particular form, such as the size, morphology, chemical structure as well as the specific application in which it is used for. The effects of graphene on the immune systems, reproductive systems, nerve systems etc. are yet to be investigated systemically. Additionally, compared to the conventional bio-degradable organic macromolecules as drug delivery carriers, graphene, being an inorganic nonmaterial's, hardly degrades into the biological system, and hence, cannot be used simply as a delivery carrier, unless some novel means are discovered to make it bio-degradable. Therefore, unless the above challenges are addressed properly, the graphene nonmaterial's-based drug delivery and therapeutic technology is not likely to hit the market in the near future, given the clinical and regulatory hurdles posed by the pharmacovigilance agencies.

Graphene and its derivatives in cell culture, tissue engineering and cell growth behavior

Graphene-based nanomaterials have been used as scaffolds for cell culture and tissue engineering and exhibited minimal harmful effect on the mammalian cells, very good adhesion properties, excellent gene transfection efficacy, high capability of the promotion of differentiation of stem cells into bone cells in a controlled manner for bone regeneration therapy, excellent boosting ability for the neurite sprouting and outgrowth

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for neural interfacing, [83,89-97]. Graphene derivatives and graphene-based nanocomposites also revealed inhibition effect of bacterial growth on their surfaces due to the synergistic effect with other materials, and the oxidative stress induced by membrane disruption. Also, the antibacterial activity is found to be controlled by the size of the graphene derivatives with minimal skin irritation [80,98-106].

Challenges

The main challenges for the graphene and its derivatives in cell culture, tissue engineering and antibacterial activities are (i) proper understanding of the mechanism underlying the stem cell differentiation, (ii) clear knowledge on the relative antibacterial activity of different graphene derivatives, (iii) proper understanding of the experimental conditions for bacterial activity, (iv) proper detection technique of the antibacterial activity to determine the cause and effect. For example, graphene showed different stem cell differentiation against its derivatives, which is assumed to be due to the different interactions between the growth agents and the graphene's (and its derivatives') surfaces. Unless the mechanism is properly known, it will be difficult to scale the technology. Similarly, some reports suggested enhancement of bacterial growth on graphene surfaces, rather than the inhibition [107], which clearly indicates the dependence of the antibacterial activity on the experimental conditions, which needs to be standardized for practical applications. Also the detection mechanism of the antibacterial activity of graphene-based nanomaterials should be done in the molecular level to understand the mechanism properly and monitor the antibacterial activity at the molecular level.

Future Prospects

The new and exciting properties of graphene and its derivatives lead to some interesting biomedical applications and dramatic progresses have been made in this direction in recent times. But this area of research is still in its infant stage and needs proper future perspective to convert into a market - oriented research field. In that sense the following future trends are noteworthy.

i)For therapeutic application of graphene and its derivatives, proper understanding of the toxicity profile of this kind of new nanomaterials *in vitro* and *in vivo* is the most important and future goal. Additionally, the future research should be directed in the combinatorial therapies which may include two or more of the following therapies like PTT, PDT, photo acoustic, photo catalytic, RF ablation etc. with the conventional therapeutic drugs to overcome the multi-drug resistance problem, to decrease the doses of drugs and reduce the side effects, which often pose hurdles in the current chemotherapies, thus improving the tumor treatment efficacy. Therefore, combined therapies based on graphene may bring a novel opportunity to the next generation of cancer treatment.

ii)Another very important future biomedical application area of graphene-based nanomaterials would be the gene transfection *in vivo*. Although several studies reported that biofunctionalized graphene derivatives could serve as gene transfection vectors *in vitro*, but *in vivo* gene delivery using graphene-based nano-vectors are yet to be explored. To realize this goal, a better and smarter design of surface chemistry, based on the unique properties of graphene and its derivatives, is necessary for future treatment of genetic disorders.

iii)Another immediate goal for graphene-based biomedical application is the synthesis of uniform graphene nanomaterials which can help increase the repeatability required for accurate biomolecules detection and drug delivery. Additionally, new and scalable (for mass production) preparation methods have to be developed for inerratic graphene-nanomaterials synthesis, and new bio-functionalization methods have to be realized to get desirable physical and chemical properties of graphene and its derivatives as well as to prevent them from agglomeration during the biomedical applications.

iv)In the field of bio-imaging, although graphene-based nanomaterials, especially graphene quantum dots (GQD) have shown great potential for its low toxicity *in vivo*, but the productivity is quite low. Therefore, future goal should be directed in investigating various techniques to increase the productivity of GQDs with high quantum yields.

v)In the field of graphene nanomaterials-based bio-sensors, the sensing efficiency is still not up to the mark for market applications. Therefore, future trend in this field should be to understand the molecular mechanism of the bio-sensors and the physical/chemical parameters related to the performance of the sensors. This will allow for the realization of more efficient, reliable and accurate graphene-based bio-sensors for practical applications.

vi)Another novel future bio-application of graphene and its derivatives is the combined bio-medical investigation and therapeutic application, which includes *in situ* localization/ detection via bio-sensing, real time monitoring/cell imaging and drug delivery. The ability of graphene-based nanomaterials in DNA adsorption, quenching and protection from enzyme cleavage may lead to the development of graphene-based nanoplatform for combined bio-sensing, bio-imaging, drug delivery and therapy.

vii)In the field of laser desorption/ionization mass spectrometry (LDI-MS), nanohybrid films of graphene nanomaterials/other carbon nanomaterials/metal nanoparticles showed enhanced LDI efficiency, having excellent applicability for LDI-MS analysis. Therefore, graphene-based nanostructure films as platforms for LDI-MS analyses for phospholipase activity, small molecules and mouse brain tissue can have interesting future applications.

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viii)In the field of antibacterial activities of graphene and its derivatives, the future research should be directed on the study of the effects of time, concentration, size, density, and surface structure of graphene nanomaterials, to understand the underlying mechanism.

ix)As far as the fields of graphene nanomaterials-based cell growth, tissue engineering and regenerative medicinal applications are concerned, since these areas of research are relatively new, special attention is needed in future to develop this field properly for novel applications. For example, graphene derivatives, supported by other bio-molecules, have shown the potential of generating mechanically strong, electro-conductive hydrogels, which can have important future application in the field of cardiac tissue repair technology.

x)Besides experimental works, theoretical investigations of various aspects of graphene and its derivatives, including electronic structure, doping effects, optical/electrical/ electrochemical/ mechanical properties and dependence of these properties on the number of layers, surface structures, functionalization etc. are the need of the hour to help understanding the properties of these new nanomaterials at the molecular level. This may lead to the rational designing of the bio-medical devices combining with theoretical modeling with advanced experimental techniques to significantly shorten the cycle of graphene nanomaterials-based biomedical research.

xi)Just like every coin has two sides, the toxicity effect of graphene and its derivatives can be exploited in a positive way by considering any particular toxicity profile arose from a certain bio-activity of graphene nanomaterials, to use in therapeutic applications like antibiotic and/or anti-cancer treatments.

xii)And last but not the least, apart from graphene, GO and rGO (pristine & bio-functionalized), which have maximum bio-medical applications, exploitation of other 'cousins' of graphene (like graphane, graphane, graphene, graphdiyne, fluoro graphene etc.) in biomedicine can become an interesting future research field. Since these new nanomaterials are still in the nascent stage, their scalable syntheses procedures, their electrical, optical, mechanical, chemical, electrochemical, electronic and surface properties, their toxicity profile and bio-compatibility etc. are yet to be explored completely and can become an open research field with tremendous potential for bio-medical applications.

Since many of the unique advantages, fascinating properties and potential applications of graphene and its derivatives are yet to be explored, interdisciplinary approaches among physics, chemistry, biology, materials science and engineering will be the need of the hour. This will not only accelerate the mechanistic understanding of graphene-based platforms for diverse bio-medical applications, but can bring these applications from the research lab to the clinic.

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