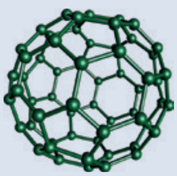
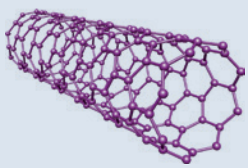
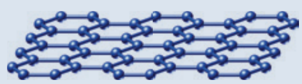
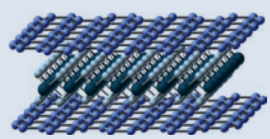
Graphene devices for life

Kostas Kostarelos and **Kostya S. Novoselov** examine the potential of graphene in biomedical applications.

The use of nanomaterials in health and life-science applications has been steadily growing[1,2]. Nanoscience could allow the creation of new approaches in medical intervention, and it promises to revolutionize established clinical practice. The design and engineering of delivery vehicles for diagnostics or therapeutics are just some examples among many; others include point-of-care ultrasensitive sensors, smart (responsive) substrates for artificial tissue design and high-specificity biomarkers. Graphene is considered the archetypal nanostructure within the family of carbon nanoforms, among fullerenes, carbon nanotubes, nanohorns, graphene quantum dots and others. Graphene materials (GMs; a family of materials including pristine graphene sheets, few-layer graphene flakes, graphene oxide and many others) offer a range of unique, versatile and tunable properties that can be creatively used for biomedical purposes. Their lateral dimensions can be adjusted between nanometres and millimetres, and their thickness can be tuned from single to hundreds of monolayers (also modulating flexural rigidity). The two-dimensional (2D) flat surface can be modified to functionalize the surface character from highly hydrophobic to patchy amphiphilic to highly hydrophilic. The tunability of such properties is perhaps unprecedented among other nanomaterials, offering immense design capabilities. Also important is that graphene can be produced relatively cheaply and in large amounts.

Graphene applications in biomedicine, even though still in their infancy, can be divided into several main areas: transport (delivery) systems, sensors, tissue engineering and biological agents (for example antimicrobials). The use of various carbon nanoforms in such biomedical applications has been actively pursued for the past decade or more[3]. Therefore, determination of the unique features offered by GMs (and other 2D structures) is of critical importance in the design and development of truly novel constructs of enhanced or previously unattainable functionality. Table 1 illustrates how the most widely explored nanocarbons (fullerenes and carbon nanotubes) compare with graphene and other 2D heterostructures in terms of their biomedical applicability and potential. It also highlights the numerous challenges that each structure faces in implementation and clinical adoption.

Table 1 | Opportunities and challenges in biomedical applications for different forms of nanocarbon.

	Fullerenes	Carbon nanotubes	Graphene materials	2D heterostructures
				
Unique properties used in biomedical and life science	Free radical scavenging	Cylindrical shape Photothermal capability Inner space (for filling)	2D flat shape Large available surface area Flexibility Electrical conductivity Absence of bandgap Aqueous solubility (in the case of graphene oxide) Versatility of chemical functionalization	Similar to graphene materials in shape and structure More variability in the 'mix' of physical properties from different single layers
Biomedical application (most mature or intensively explored)	Antimicrobials	Molecular transporters (drug delivery) Near-infrared imaging agents	Highly sensitive biosensors Molecular transporters Coatings/substrates for tissue engineering and implants	Almost no such applications reported Biosensing and biodetection will be prime candidates
Opportunity	Interaction with double-stranded nucleic acids (for example mitochondrial DNA)	Translocation of biological membranes and barriers	Responsive to a wide range of parameters High sensitivity Multiple read-out routes Ease and speed of degradation	'Fabricate-by-design' based on the selection of layers
Challenge	Aqueous dispersibility Non-specific DNA binding leading to cytotoxicity	Controlled manufacturing and surface functionalization Aqueous dispersibility Adverse (inflammatory) responses related to fibre shape Slow kinetics of biodegradation	Unknown cytotoxic limitations Controllable dimensions Determination of *in vivo* biodegradability kinetics	Interaction with biological matter is currently unknown

So far, designs of delivery systems based on GMs have primarily attempted to make use of their very large surface-to-volume ratio (larger than with most other materials) and their facile chemical modification. By careful tuning of the dimensions and hydrophobic/hydrophilic surface character of GMs, one can potentially control their capacity to translocate or interact with different biological barriers (for example, membranes or the glomerular filter). Also, the razor-like shape of graphene sheets can potentially help them to slide through membranes and become internalized in a cell. Some evidence of such capacity for particular GM types has been reported[4], but there is still a lack of mechanistic description of the way in which different GMs interact with biological barriers.

It is also possible to consider the graphene flake itself as a therapeutic agent. Research efforts are currently focused on exploring different GM types as local heat sources activated on laser irradiation to ablate tumour tissue by hyperthermia[5]. The absence of a bandgap makes GMs sensitive to irradiation across a wide spectral range, therefore enhancing options for the design of such agents. Antimicrobial activity (bacteriostatic and bacteriolytic) is another biomedical application that is based on the inherent properties of GM sheets themselves, even though there have been contradicting reports about the inherent antimicrobial activity of different GMs[6–8]. For all therapeutic applications in which administration of GMs is envisioned, because the dimensions, surface chemistry and hydrophilicity/hydrophobicity of graphene flakes can vary widely, it will be imperative to understand their impact on some fundamental pharmacological parameters (for example, blood circulation kinetics, immune cell interactions and responses, and tissue distribution) before they can be tuned to achieve transport to a specific location in the body.

Graphene-based sensor development is another area of application being intensively researched[9]. Because all graphene properties are interlinked (for instance chemical modification will change its electrical resistance, and strain applied to it can be directly detected through the Raman spectrum), it could be possible not only to sense a wide range of parameters, but also to provide a large choice of read-out methods (for instance, chemical doping can be easily detected by transport, optical or Raman measurements). Most promising are the fast biological sensors with either electrical or optical (plasmonic) read-outs in which selectivity is ensured by chemical functionalization. As graphene simultaneously plays the role of a sensing surface (which can be funtionalized to increase selectivity) and the conducting channel, its sensitivity can potentially be very high (note that in many traditional sensors based on field-effect transistors, the conducting channel is separated from the sensing surface)[10]. The other interesting directions in the design of GM-based devices include DNA sequencing through nanopores[11] and the use of graphene as a photodetector or in plasmonic chemical sensors[12]. The maturation and time-to-market of graphene-containing biosensor devices that will not require direct administration into patients are expected to be much more rapid than for administered therapeutics or diagnostics.

Graphene has also been proposed for coating or fabricating matrices and substrates for the engineering of various artificial tissue components and implants. Some of the most promising are artificial skin and orthopaedic implants[13]. Graphene and graphene oxide membranes can also be engineered in different thicknesses and with different chemical functionalities that could allow controllable permeation of different molecules[14]. It is also conceivable to impregnate graphene-containing membranes with specific (therapeutic) chemical species and release them controllably[15,16].

It should be clear that all these biomedical applications, although actively researched, are still in the early stages of development. A distinction in expectations should be made among different types of device incorporating GMs, mainly determined by the risk–benefit ratio that each particular medical need and application allows[17]. ❐

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Graphene in the sky and beyond

Emilie J. Siochi explains how most of the properties of graphene could be of use in aerospace applications.

With the premium placed on strong, lightweight structures, carbon materials have a long history of use in aerospace applications. Graphitized carbon and carbon–carbon composites[1] are used in thermal protection systems and heat shields, carbon fibre composites are used in aircraft[2], and more recently, carbon nanotubes have been used on spacecraft[3]. As the newest member of this family of materials, graphene also has interesting properties that intersect with unique aerospace requirements. Despite their many attractive aspects, graphene-based structures and systems, like any other material used in aerospace, must clear a number of hurdles before they will be accepted for use in flight structures. Carbon fibre, for example, underwent a development period of several decades between initial discovery and large-scale application in commercial aircraft[4].