Translating graphene and 2D materials into medicine

Kostas Kostarelos

Adoption of graphene and other 2D crystals in biomedicine is challenging — some guidelines to facilitate this process and avoid inflated expectations should be considered.

Advanced materials are key contributors to the development of next-generation medical technologies. The advent of carbon-based nanostructures and 2D materials has generated a wealth of previously unavailable nanoscale systems with unique and unexpected physicochemical properties. Translating their exceptional material characteristics into functional devices that clinicians and health professionals would deem problem solvers is not easy. The success of this process will depend on how well the community is able to exercise 'measured expectations' to allow scientific knowledge to gradually mature into robust technologies for clinical use.

Materials in the flatland

Graphene is the newest member of the family of carbon nanomaterials, which includes fullerenes, nanotubes, nanohorns and dots, to name a few. What makes graphene fundamentally unique is the underlying concept of a stable, free-standing nanoparticle in the form of a single-atom, 2D flat sheet. Graphene is the archetypal nanostructure in a rapidly populated landscape of flat materials made of building blocks beyond carbon — boron, silicon, phosphorus or polymer crystals — and that are currently reported at a weekly rate[1,2]. Indeed, it has become very popular in materials science to attempt to exfoliate any type of bulk material to produce 2D sheets from it.

How does biomedical science feel the impact of these frenzied 'flatland' developments in materials research? It has to be acknowledged that biomedicine has always been a late starter when it comes to the utilization and eventual adoption of advanced materials. For example, it took lipid-based vesicles (liposomes) almost 30 years to develop into a clinically used blood-circulating drug-delivery vehicle. During my recent visit at MIT, Bob Langer recalled that in the 1970s almost the entire biomedical and chemical communities considered his attempts to translate polymers (or plastics, as they called them then) into implantable or injectable devices to be 'prophetic fiction' with no realistic chances of clinical translation. This attitude is partly due to an innate conservative approach towards the adoption of new technologies in medicine because of the need for stringent safety studies, the significant costs associated with the clinical development of a new technology and the resulting high attrition rate of new discoveries that translate into successful clinical applications. These issues need to be taken into consideration when developing a new technology for clinical use, irrespective of how groundbreaking the innovation may be.

Graphene's great expectations

Despite its conservative aptitude, biomedicine is becoming increasingly interested in exploring and supporting the adoption of graphene-related 2D layers in a range of applications and designs[3,4]. Although the global research activity in medicine still represents only a small fraction of the overall efforts in the study of graphene and other 2D materials — the applications in composite materials and electronics are considerably more mature — we are observing an exponential growth in the accumulation of new knowledge on the role graphene may have in medicine. Currently, there are two main trends in the adoption of graphene in biomedicine. First, there is an increasing wealth of graphene-incorporating devices (such as sensors and implants) engineered for various applications. Second, highly oxygenated and structurally defected graphene oxide sheets and their derivatives, which are dispersible in water and easily functionalized, are currently the materials of choice for applications in which suspensions of graphene-based sheets are studied in physiologically relevant media, in cell cultures or *in vivo* (for example, in studies for drug delivery, pharmacology and toxicology).

In the context of the Graphene Flagship project, we were delighted to see the initiation of research in biomedical technologies in the recently launched next phase of the project[5]. This phase focuses on the incorporation of 2D materials in devices for neural interfaces, in particular towards the industrially and clinically adoptable application area of high-precision neurological recording and stimulation.

Nanomedicine Lab, Faculty of Biology, Medicine & Health and National Graphene Institute, University of Manchester, Manchester, UK.

kostas.kostarelos@manchester.ac.uk

Article number: 16084
doi:10.1038/natrevmats.2016.84
Published online 25 Oct 2016

A short guide to translation

The challenges of translating graphene and other 2D materials into biotechnology and biomedicine are not new or unfamiliar. Similar challenges have dominated the development of every cutting-edge technology in the biomedical field, testing the patience of investors, clinicians, patients and politicians. Gene therapy, stem cell therapeutics and genome editing are only three recent examples.

Despite some clear advantages and opportunities offered by 2D materials — such as their unprecedented physicochemical properties, the variety and versatility afforded by different 2D crystals, and their wide availability and low cost, which will facilitate the upscaling of their production — the adoption of 2D materials by industry and clinical practices will require perseverance.

A shortlist of key strategies that could facilitate the industrial and clinical translation of 2D materials is discussed below.

Know your material. Before any serious effort can be undertaken in the translation of 2D materials into biology and medicine, a careful characterization of the properties of the material is essential, as is their reproducibility. Currently, the literature is littered with studies that provide frivolous (if any) analysis and understanding of the 2D materials used, and yet report definitive and at times spectacular behaviours and performances in biologically relevant environments. This creates a chaotic landscape that hinders scientific and technological progress, while compromising the credibility of the whole community in the eyes of potential industrial and clinical adopters.

Create knowledge and technologies, not products. Although research programmes should have specific goals towards the development of clinically relevant products, significant gaps remain in the fundamental biological understanding of 2D materials. The interaction between cells and 2D sheets, the pharmacokinetic profiles of these materials, and the reactions of different types of cells and tissues when exposed to them are only some examples of what remains not completely understood for products to be developed.

Engage with end users as early as possible. Researchers developing 2D materials for medicine need to engage with clinicians, industrialists, patient groups and regulatory authorities from the very early stages of their projects. Translation of novel, advanced technologies can only succeed if all of the stakeholders are able to contribute to the steering of the development of these new technologies in directions that will minimize stumbling blocks in the later stages of clinical translation.

Niche applications will break the translation ceiling first. As with other groundbreaking technologies (such as cell or gene therapeutics), clinical translation of 2D materials will need to take place incrementally, starting from focused application areas and niche diseases that may not necessarily command the market share that investors initially aim for. This should be considered as the natural progression towards more widespread clinical adoption — a graphene-based cure for cancer might be developed, but within a much longer time frame. Biosensing devices that interact with the sample fluids of a patient *ex vivo* have the potential to be translated relatively quickly; however, it can be debated whether such applications will constitute revolutionary advances in medical practice.

Measured expectations. Overestimating the potential of a technology and building unreasonable expectations around it is a common mistake, mainly driven by the excitement of newly available opportunities and by the desire to exploit them. The example of the tremendous hype generated by gene therapeutics and by the Human Genome Project in the late 1990s, which was not met by correspondingly sparkly clinical outcomes, is telling. In the case of 2D materials, the publicity ensured by the multiple awards captured by researchers in the field — mainly motivated by the unveiling of the fundamental physical principles that govern these materials — has created an anticipation that should be managed carefully. In the case of the biomedical applications of 2D materials, the expectations are growing fast. However, it is important to manage them realistically to avoid a backlash when obstacles arise, as they will, when the first applications move closer to clinical use.

Conclusion

The tremendous interest in the translation of graphene and other 2D materials into a range of application areas, including biotechnology and biomedicine, is creating a feeling of great excitement. This momentum needs to be managed carefully in the lengthy and expensive road to clinical translation by setting realistic expectations and tangible goals, because the process will require decades of persistent effort.

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Competing interests statement
The author declares no competing interests.

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Graphene Flagship: http://graphene-flagship.eu/
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