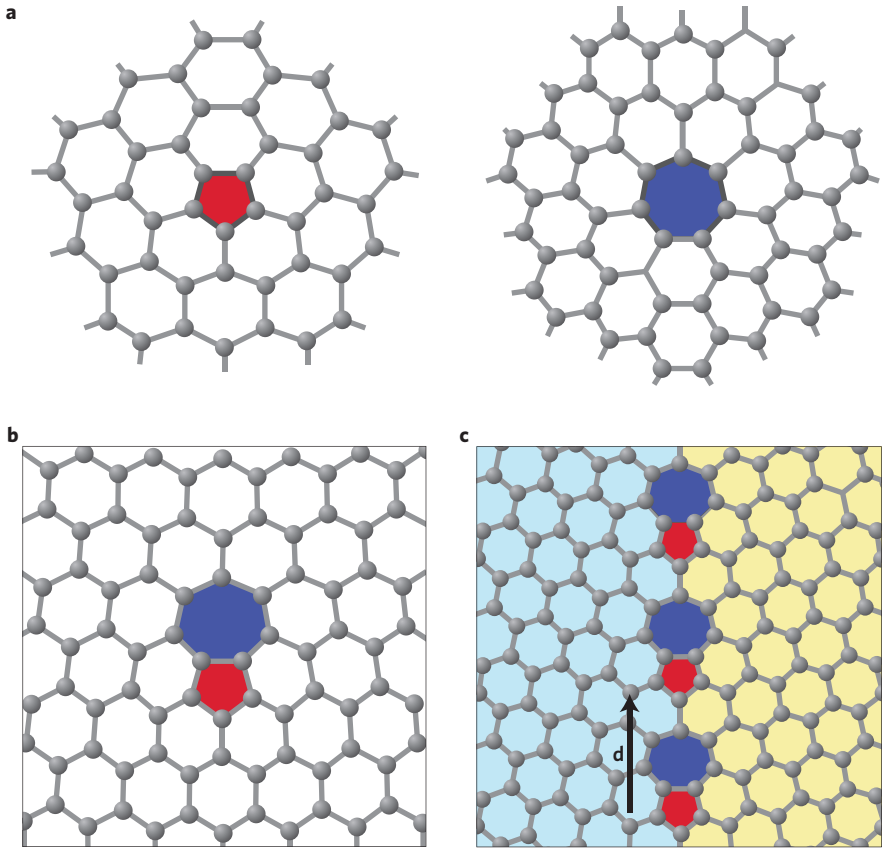

Figure 1 | Topological disorders in graphene. **a**, Left: positively charged disclination. Right: negatively charged disclination. **b**, Edge disolocation where combining the positive and negative disclinations results in the addition of an atomic row. **c**, Grain boundary formed by a periodic array of edge dislocations with a periodicity defined by the vector **d**.

a careful study of this grain structure is necessary to understand transport in large-area polycrystalline graphene samples. Moreover, if type II boundaries can be engineered in these samples, the tunable energy gaps that form at the local boundary region could be utilized in future graphene electronics.

Although this first important step has been made, a complete understanding of the electronic structure of graphene grain boundaries is still far away. In realistic graphene grain boundaries, the periodic arrangement of dislocations assumed in the authors' work may not be achieved. Randomly oriented grain-boundary segments with complicated dislocation arrangements may be more common features. Any type of disorder breaking the translational periodicity would then result in electronic transmission within the transport gap of the perfectly reflecting type II grain boundaries. The magnitude of this induced transmission would depend on the concentration of such disorder, and may eventually lead to finite conduction within the transport gap of pristine grain-boundary structures. Further experimental and theoretical studies with realistic atomic-scale defects will surely help clarify what happens in realistic samples. ❐

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Reference

1. Novoselov, K. S. *et al. Science* **306,** 666–669 (2004).
2. Reina, A. *et al. Nano Lett.* **9,** 30–35 (2009).
3. Li, X. *et al. Science* **324,** 1312–1314 (2009).
4. Bae, S. *et al. Nature Nanotech.* **5,** 574–578 (2010).
5. Yazyev, O. V. & Louie, S. G. *Nature Mater.* **9,** 806–809 (2010).
6. Yazyev, O. V. & Louie, S. G. *Phys. Rev. B* **81,** 195420 (2010).
7. Chico, L., Crespi, V. H., Benedict, L. X., Louie, S. G. & Cohen, M. L. *Phys. Rev. Lett.* **76,** 971–974 (1996).
8. Dresselhaus, M. S., Dresselhaus, G. & Eklund, P. C. *Science of Fullerenes and Carbon Nanotubes* (Academic, 1996).

CARBON NANOTUBES

Fibrillar pharmacology

The mechanisms by which chemically functionalized carbon nanotubes flow in blood and are excreted through the kidneys illustrate the unconventional behaviour of these fibrillar nanostructures, and the opportunities they offer as components for the design of advanced delivery vehicles.

Kostas Kostarelos

In recent times, a wide variety of filamentous, fibre-like nanostructures have been isolated or synthesized, and subsequent attempts have been made to use them in biomedical applications. Such nanostructures can be naturally occurring, protein-based constructs of specific biological activity, for example viruses and amyloid fibrils, or engineered materials such as nanofibres, filomicelles and nanotubes.

Fibrillar nanostructures are gaining importance in biomedical research to further our understanding both of the mechanisms involved in pathological conditions (infectious processes or neurodegeneration) and of the interactions between nanoparticles and the biological milieu. In a more practical sense, filamentous nanomaterials are designed as transporters of therapeutic and/or diagnostic agents with much-wanted control over their *in vivo* tissue navigation, cargo release and clearance profile.

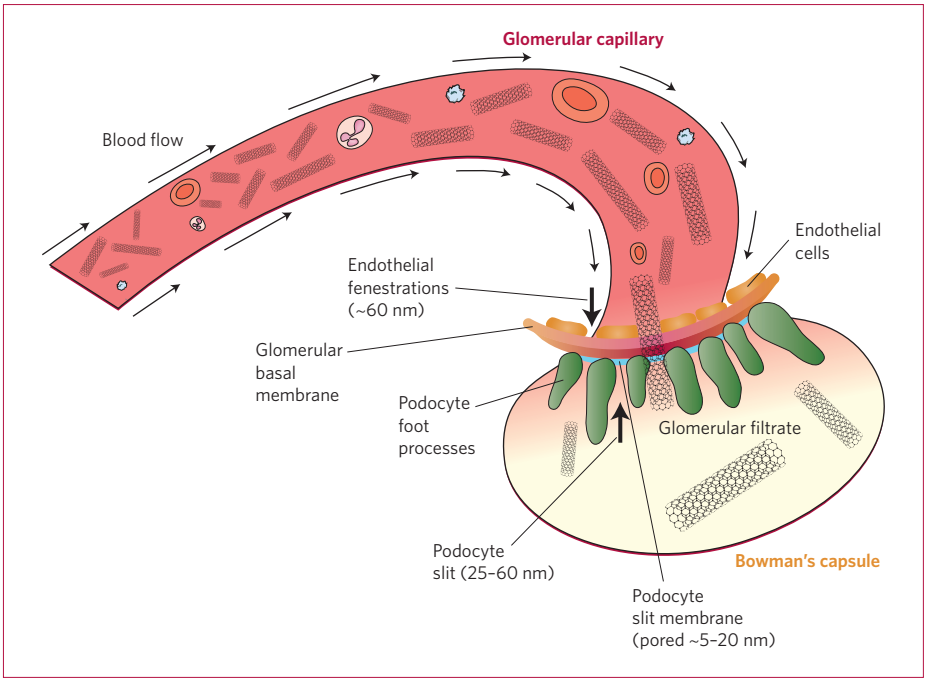

Figure 1 | A schematic of the glomerular filtration system (a multicompartmental structure). The system is believed to act synergistically, with no single most important filtering component. Some types of chemically functionalized carbon nanotubes can translocate through the filter, but not all carbon nanotubes and filamentous nanoparticles will be expected to translocate in this way. The surface properties (for example, charge, polymer coating) and structural characteristics (for example, diameter, flexibility) of the nanotubes play an important role in their transport and elimination properties.

The tissue distribution, accumulation and excretion of nanomaterials are dynamic processes that determine the balance between pharmacological activity and unwanted toxicity. The mechanisms of these processes have been extensively debated and remain unclear, although they evidently depend on nanoparticle characteristics such as molecular weight and surface charge.

Ruggiero *et al.* report in the *Proceedings of the National Academy of Sciences* the mechanisms of elimination of one such type of engineered filamentous nanostructure — functionalized single-walled carbon nanotubes (SWCNTs)[1]. The SWCNTs are decorated with various ligands, by covalent functionalization, such that renal clearance of the materials in mice can be monitored using three different imaging techniques. The study offers mechanistic explanations, both experimental and theoretical, of how SWCNTs can align with flowing blood and be rapidly excreted through the renal filter. These findings have implications for our fundamental understanding of renal physiology and our knowledge of the ability of chemically functionalized SWCNTs to translocate biological barriers[2]. The latter is an important consideration in the design of nanomaterials for both therapeutic and diagnostic purposes, and in determining health risks posed by their biomedical use.

Removing waste products from the bloodstream of the human body is the principal task of the kidneys, and within these organs a process termed glomerular filtration acts as the 'gate-keeper' (Fig. 1). Blood enters the kidneys through the renal artery and flows into glomerular capillaries. Any circulating matter passes through these capillaries and can be transported, by diffusion or osmosis, into the Bowman's capsule where the glomerular filtrate (also commonly referred to as 'primary urine') is collected. Although reabsorption of molecules into the bloodstream can occur after this process, this is the makings of urine that will be eventually excreted by the body. The glomerular filter is a multicompartmental structure composed of endothelial cells, the glomerular basal membrane and podocyte foot processes (Fig. 1). Similar to transport across any membrane, there was thought to be a maximum size limit for molecules that could cross this structure[3]. Until recently, the threshold — in terms of molecular weight — was believed to be around 50 kDa. Now, Ruggiero *et al.* describe how chemically functionalized SWCNTs with average lengths in the range of 200–500 nm, and hence molecular weights of up to 500 kDa, are eliminated by rapid translocation through the glomerular filter following intravenous administration, without signs of degradation. More importantly, Ruggiero *et al.* show that no active transport mechanism is responsible for this overwhelming glomerular translocation and that SWCNTs follow rapid, 'first-pass' pharmacokinetics that eliminates most of the injected dose from the body within minutes. Only a small fraction (~15% of injected dose) is reabsorbed into the tubule cells of the kidneys and presumably, though not shown experimentally, recycled into the bloodstream, leading to slower, second-phase, excretion rates. Moreover, the theoretical analysis presented illustrates the importance of nanotube shape and aspect ratio, in allowing alignment with flowing blood and hence, orientation of fibrils perpendicular to the glomerular filter.

Previous investigations of tissue distribution and blood clearance kinetics of the same chemically functionalized single-[4] and multiwalled carbon nanotubes[5] following intravenous administration had shown the rapid renal clearance and translocation across the glomerular filter[6]. However, these results had elicited, along with excitement, some scepticism because other studies using carbon nanotubes modified with polymeric molecules[7] or with different surface chemistries[8] reported contradictory data, with liver accumulation and slow hepatobiliary excretion. Now, Ruggiero *et al.* reveal the unexpected mechanisms for rapid renal clearance of these highly functionalized materials and remove all doubts of their unique pharmacological behaviour.

The translocation of filamentous SWCNTs across the glomerular filter warrants further investigation and a multidisciplinary approach to understand various aspects of this intricately complex process. For example, new fluid dynamics formulae are required to explain the blood transport of filamentous nanoparticles, and revised glomerular pathophysiology models are needed for filamentous, nanoscale objects. Also, the characteristics of carbon nanotubes that determine such biological effects and the dynamic interactions between flowing, filamentous objects and blood components (for example serum proteins[9]) remain in need of investigation. Finally, whether filamentous nanoparticles maintain their capacity to align with blood flow and be renally excreted after accumulation within a tissue (for example liver, brain or tumour) will greatly determine their toxicological profile[10].

Rapid elimination from blood circulation and urinary excretion may be desirable from a toxicological point of view, but perhaps undesirable therapeutically when the aim is to achieve biological activity at specific diseased sites. Therefore, a balance between longer blood circulation and maintenance of renal excretion should be envisaged as one of the optimal (but challenging) strategies for the design of transporters based on carbon nanotubes. In a broader context, considering our accumulating knowledge on the pharmacokinetics of carbon nanotubes and that of other filamentous nanomaterials[11,12], it is evident that the blood flow kinetics and transport mechanisms of these high-aspect-ratio materials are very different from those of spherical nanoparticles.

Overall, the wealth of design options that are offered by different engineered nanomaterials, for example by controlling shape, size, surface properties and molecular weight, makes it possible to fabricate materials that interact in widely differing ways with biological matter. Applying this principle, specific features can be included on nanotubes and other fibrillar nanostructures to achieve certain biological activities and eventually therapeutic or diagnostic outcomes. ❐

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References

1. Ruggiero, A. *et al. Proc. Natl Acad. Sci. USA* **107,** 12369–12374 (2010).
2. Kostarelos, K. *et al. Nature Nanotech.* **2,** 108–113 (2007).
3. Haraldsson, B., Nystrom, J. & Deen, W. M. *Physiol. Rev.* **88,** 451–487 (2008).
4. Singh, R. *et al. Proc. Natl Acad. Sci. USA* **103,** 3357–3362 (2006).
5. Lacerda, L. *et al. Adv. Mater.* **20,** 225–230 (2008).
6. Lacerda, L. *et al. Small* **4,** 1130–1132 (2008).
7. Liu, Z., Tabakman, S., Welsher, K. & Dai, H. *Nano. Res.* **2,** 85–120 (2009).
8. Deng, X. *et al. Carbon* **45,** 1419–1424 (2007).
9. Cedervall, T. *et al. Proc. Natl Acad. Sci. USA* **104,** 2050–2055 (2007).
10. Kostarelos, K. *Nature Biotechnol.* **26,** 774–776 (2008).
11. Geng, Y. *et al. Nature Nanotech.* **2,** 249–255 (2007).
12. Park, J. H. *et al. Small* **5,** 694–700 (2009).

MATERIAL WITNESS

OYSTER GLUE

In 1880, Chesapeake Bay was heaven for oyster-lovers, as the native common Eastern oyster *Crassostrea virginica* was hauled ashore in about a hundred times the quantities now harvested. But over-fishing has so devastated the population that non-native varieties have lately been introduced, albeit with little success.

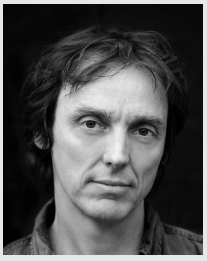
It's the same story the world over. Along the coasts of Europe and Australia too, oyster populations have been reduced to less than 10 percent of their historical abundance[1]. This is not just a gastronomic disaster, for oyster reefs — agglomerated mounds of billions of oyster shells — are a vital component of estuarine and coastal marine ecosystems. The reefs harbour other aquatic organisms, filter the sea water, and help protect the coastline from storms. The shift in the ecological balance has also led to eutrophication of estuarine waters.

Last year brought a ray of light to this gloomy picture, when researchers reported that artificial reefs constructed since 2004 in estuarine sanctuaries in Chesapeake Bay from the shells of native *C. virginica* dumped by the US Army Corps of Engineers have helped to boost oyster populations[2] — not to the levels of a century ago, but enough to demonstrate the potential of the method.

This study showed that the higher the artificial reef (the highest were up to 45 cm above the river bottom), the more effectively it stimulated oyster growth. Reefs are not, however, simply piles of old shells: they have a complex architecture in which shells are bonded together by material excreted by the living oysters. The research showed that the long-term stability of a reef depends crucially on whether it acquires enough cohesion from this cement.

That's why a new study of the adhesive used for oyster-reef construction could prove so important. Burkett *et al.* have analysed the chemical composition of this material in *C. virginica* reefs offshore from South Carolina[3]. They find that it is an organic–inorganic composite made up mostly of calcium carbonate deposited within a matrix of phosphorylated protein.

There is less of the mineral in the adhesive (about 20 percent) than in the oyster shells (about 30 percent), and moreover it is a mixture of the polymorphs calcite and aragonite in the ratio 2:1, whereas the shell is mostly calcite. So the inorganic component of the adhesive is clearly tailor-made. And the glue as a whole is very different from that used by mussels and barnacles to stick to surfaces, which is mostly protein. Mussel adhesive proteins in particular have inspired biomimetic efforts to create resilient polymeric adhesives[4]. Both these and barnacle glues (which are less well understood) are strongly hydrated, whereas the inorganic–organic material of oysters has only a tenth of the water content of barnacle adhesive.



PHILIP BALL

As well as suggesting a new strategy for biologically inspired adhesion — and, on the other hand, for preparing antifouling coatings for marine structures — the new findings might offer critical information for promoting the integrity of artificial reefs, which could become central to restoring this vital component of coastal ecology. ❐

References

1. Kirby, M. X. *Proc. Natl Acad. Sci. USA* **101,** 13096–13099 (2004).
2. Schulte, D. M., Burke, R. P. & Lipcius, R. N. *Science* **325,** 1124–1128(2009).
3. Burkett, J. R., Hight, L. M., Kenny, P. & Wilker, J. J. *J. Am. Chem. Soc.* **132,** 12531–12533 (2010).
4. Lee, B., Dalsin, J. & Messersmith, P. in *Biological Adhesives* (eds Smith, A. M. & Callow, J. A.) 257–278 (Springer, 2006).