Challenges and optimism for nanoengineering

Tomas Mustelin
*Infectious and Inflammatory
Disease Center and Cancer
Center, The Burnham
Institute for Medical
Research, 10901 North
Torrey Pines Road, La Jolla,
CA 92037, USA
Tel.: +1 858 713 6270;
Fax: +1 858 713 6274;
E-mail: tmustelin@
burnham.org*

'...the best reason for optimism is that life has already solved the obstacles we are grappling with and produced 'nanodevices' with capabilities that far exceed the ones nanomedicine is hoping for.'

Recent advances in nanotechnology and materials science have made it possible to design and synthesize structures with nanometer-scale features that have the potential to interphase in novel and productive ways with cells and tissues. Further progress in this field in the near future will probably result in more sensitive and complex biosensors, refined drug targeting, *in vivo* diagnostic applications and, eventually, novel avenues for the treatment of human diseases, many of which are presently refractory to the small-molecule drugs currently available. This editorial discusses some of the prospects and main obstacles for nanomedicine. I propose that the new field of nanoengineering should turn to the nanoscale features of biology to learn how to design nanodevices for therapeutic uses. In my view, the best reason for optimism is that life has already solved the obstacles we are grappling with and produced 'nanodevices' with capabilities that far exceed the ones nanomedicine is hoping for.

Biology could well be defined as the science of nanostructures made of predominantly carbon, oxygen, nitrogen and hydrogen. Indeed, it is their subnanometer structural features that give biomolecules their properties and allow them to self-assemble into functional units with the autonomous and self-replicating properties we call 'life'. In the last century we have come a long way in our quest to understand how biomolecules work and how their smallest errors can be associated with severe human disease. By contrast, we have not yet advanced far at all on the road to learning how to repair cellular machinery. Currently, the best avenue for therapy of human disease consists of small-molecule enzyme inhibitors – drugs, many of which are nonselective and have

poorly understood mechanisms of action. Most drug molecules are too small to have the very high degree of specificity that biological structures typically have and, therefore, usually affect many other biomolecules than those intended. Drugs typically lack cell targeting and distribute throughout the organism, affecting every cell in the body, whether diseased or not. Most drugs can only inhibit, not stimulate (unless by inhibiting something), and can certainly not repair. Finally, drugs are extremely risky and costly to bring to the market. The long-term solution to these shortcomings is likely to emerge from the new and developing field of nanomedicine [1], in the form of more complex nanostructured materials that can interact in more sophisticated and specific ways with biomolecules to support, affect or even repair the cell's machinery.

Interactions of cells with nanomaterials. The interaction of live cells with synthetic nanomaterials is still a very poorly understood field and much empirical work is still required. However, it is already clear that when materials have nanoscale features, one cannot predict from their known chemical and physical properties how they will interact with live cells. Indeed, the nanoscale features are the ones that cells respond to. For example, cells cultured on artificial nanostructured surfaces replicate and look quite different depending on the nature of the nanofeatures of the material. Chemically inert materials made of carbon can have vastly different effects on cells depending on the nanostructure of the material: amorphous carbon is nontoxic to cells even at very high concentrations, while carbon nanotubes can damage and kill cells at much lower concentrations [2–4]. The world of natural materials also abounds in biomolecules made of the usual carbon, oxygen, nitrogen and hydrogen, but with highly toxic properties, such as ricin or tetrodotoxin, which can kill cells at minute concentrations. The point is, the nanoscale features are the critical ones. It therefore seems clear that nanomedicine must focus on nanometer- or subnanometer-sized structure, not on

the material *per se*. In other words, the same biological effects could probably be achieved by many different materials if they had identical nanosized structural features. The choice of materials to work with may then depend on convenience and the availability of technologies to utilize them.

'We need to narrow the gap between the synthetic accomplishments of biological systems and our own abilities to engineer nanodevices that can interface with those made by cells.'

Building blocks for nanomedicine

Durable, inherently nontoxic and chemically very stable (compared with cellular biochemistry) materials that appear promising for nanomedicine include silicon- and carbon-based nanomaterials, synthetic polymers and gold. These already exist in molecular forms that have nanometer-sized regularity, such as carbon nanotubes, fullerenes, silica nanobeads, silica nanowires and gold spheres, each with unique physical and chemical properties. These may be used as building blocks for a bottom-up assembly strategy, perhaps using biological molecules, such as peptides and nucleic acids [5–8], as site-specific tags and/or contact points. Biological systems abound in examples of how to assemble building blocks into complex nanomachines with a remarkable fidelity. The same principles could be used for the construction of nanodevices.

One of the main obstacles to nanomedicine today is the lack of technologies to precisely control the synthesis of nanodevices, particularly more complex ones that may begin to resemble biomolecules. This obstacle is relatively unique to nanotechnology: the desired structures are much too small for existing micromachining or etching techniques, but too large and complex for traditional chemistry. The probable solution to this dilemma will consist of the development of novel physical and chemical technologies for the synthesis, purification and characterization of nanometer-sized components ('building blocks') that have precisely uniform sizes and shapes and by the careful assembly of these into more complex nanodevices in a controlled, tunable and reproducible manner. These new technologies could perhaps be collectively called 'nanoengineering'.

Nanoengineering

Before truly sophisticated nanodevices with the potential to become a serious avenue for the treatment of patients can be created, the following major challenges have to be overcome:

- Novel technologies will be required for the precise control over nanoscale building block synthesis and the physical separation of the desired structures from imperfect structures, byproducts, catalysts or starting materials. These technologies also need to create sufficiently large numbers of identical nanostructures. Biological systems manufacture such building blocks continuously in a massively parallel manner and at high synthetic rates, but with incredibly high fidelity. We must find ways to reproduce this ability for artificial materials;
- Much more complex nanodevices will be required. We need to narrow the gap between the synthetic accomplishments of biological systems and our own abilities to engineer nanodevices that can interface with those made by cells. New approaches need to be developed for the assembly of simple nanostructures into complex, yet precise, nanomachines of potential medical use. The assembly of these devices must be reproducible and scaleable. The highest possible quality of the final product must be ensured by techniques for quality control and removal of imperfect devices;
- Issues of biocompatibility and toxicity need to be explored. Many inorganic materials used today for non-medical nanotechnology are not stable in biological fluids and yield toxic breakdown products, limiting the number of materials that can be used for biological applications. Little work has as yet been performed to determine how various nanomaterials affect cells when used at concentrations that would be medically relevant and in forms that would be present in nanodevices. The best promise lies in either chemically inert material (e.g., carbon or silica) or biological materials that yield harmless breakdown products, as well as in the expectation that exceedingly small chemical amounts would be included in the total number of nanodevices needed for significant effects *in vivo*;
- We must learn much more about how cells respond to and interact with artificial structures. Although the interactions of cells with the extracellular matrix are relatively well understood, there is very little known regarding

interactions of cells with carbon- and/or silica-based artificial materials, particularly materials that can enter the interior of the cell.

‘Little work has yet been performed to determine how various nanomaterials affect cells when used at concentrations that would be medically relevant and in forms that would be present in nanodevices.’

The solutions to these challenges will enable us to construct nanodevices that can interface with live cells in all the different ways that biomolecules do. Cell type-specific targeting, cellular entry, subcellular targeting, modulation of any cellular process and even support and repair will all be fully possible. Notably, a nanodevice does not need to be very complex to have an enormous influence on cells – think of what some of the simplest viruses can do to a cell. In fact, the first medical nanodevices may well be modeled on viruses (but without their self-replicating ability).

Conclusion

Although there are already many examples of nanotechnology in medicine, such as contrast media, drug-delivery systems, gene therapy

devices and many new promising avenues for targeting of drugs to cells and tissues, the real promise of nanomedicine is still at least a decade away. In my view, the best reason for optimism is that life has already solved the obstacles we are grappling with and produced ‘nanodevices’ with capabilities that far exceed the ones nanomedicine is hoping for. Thus, biological systems should be studied carefully from a structural and nanoengineering point of view and we should attempt to copy the designs and solutions perfected by nature. It will be some time before we learn how to build nanodevices that can interact with cells, or within cells, the way that biological macromolecules do and with the precision and fidelity that would be required for approval by any federal regulatory drug agency. The necessary technological breakthroughs will probably come from several different fields of science: materials science, physics, organic chemistry, molecular biology, cell biology and medicine. Indeed, experts in these fields are now working to find a common language and have begun to gather into interdisciplinary teams that work together to accomplish the technological and conceptual advances that are needed to push nanomedicine into the era of molecular therapeutics with the abilities that, until recently, seemed like science fiction.

Bibliography

1. Nanomedicine: grounds for optimism, and a call for papers. *Lancet* 362, 673 (2003).
2. Shvedova AA, Castranova V, Kisin ER *et al.*: Exposure to carbon nanotube material: assessment of nanotube cytotoxicity using human keratinocyte cells. *J. Toxicol. Environ. Health A* 66, 1909–1926 (2003).
3. Park KH, Chhowalla M, Iqbal Z, Sesti F: Single-walled carbon nanotubes are a new class of ion channel blockers. *J. Biol. Chem.* 278, 50212–50216 (2003).
4. Bottini M, Bruckner S, Nika K *et al.*: Multi-walled carbon nanotubes induce T lymphocyte apoptosis. *Toxicol. Lett.* 160, 121–126 (2006).
5. Li S, He P, Dong J, Guo Z, Dai L: DNA-directed self-assembling of carbon nanotubes. *J. Am. Chem. Soc.* 127, 14–15 (2004).
6. Chworos A, Severcan I, Koyfman AY *et al.*: Building programmable jigsaw puzzles with RNA. *Science* 306, 2068–2072 (2004).
7. Liao S, Seeman NC: Translation of DNA signals into polymer assembly instructions. *Science* 306, 2072–2074 (2004).
8. Yan H: Nucleic acid nanotechnology. *Science* 306, 2048–2049 (2004).