as functionality in a low-pH environment. Finally, by showing that the expression of green fluorescent protein (GFP) could be suppressed in GFP-transgenic mice, the authors established that sustained knockdown of gene expression was possible by administering the nanoparticles directly to the female reproductive tract in mice (Fig. 1b). After vaginal administration, a significant decrease in fluorescence intensity was observed in various areas of the tract for up to 14 days.

RNA interference is undoubtedly one of the greatest breakthroughs in biology in recent years. So popular is this field that a quick search for 'RNA interference' or 'siRNA' in Medline (a free online database containing bibliographic information on life sciences and biomedical publications from 1965) reveals an explosion of citations, from only about 200 in 2000 to more than 30,000 at present. This trend will surely continue to grow as the restrictions imposed by delivery are resolved through the development of more efficient and effective methods. The work of Saltzman *et al.* provides strong evidence that PLGA-mediated delivery is a viable route for localized siRNA delivery. It seems logical to predict that the effectiveness of this approach in the female reproductive tract could ultimately be extrapolated to other delicate areas of the body in which localized siRNA delivery is needed, such as the eyes and rectum. Previously, it has been shown that modifying the surface of drug-carrying PLGA particles with poly(ethylene glycol) can facilitate diffusion through mucosal barriers[9]. It is therefore reasonable to expect a certain degree of synergy by combining these two approaches, leading to highly efficient, siRNA-based localized delivery systems in the near future. ❐

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MATERIAL WITNESS

WHAT MAKES NANOMACHINES WORK?

PHILIP BALL

Since the notion of molecular machines became popular in the 1980s, a profusion of such devices has been reported. Some early examples were rotaxanes — hoops jumping on axles — but we now have DNA motors and walkers, light-driven propellers and even molecular cars. What just about all these devices have in common is that they can reversibly switch between two or more relatively stable conformations, a characteristic that is of course echoed in the molecular machines abundant in the natural world made from proteins and nucleic acids.

Not all proteins are 'machines' — structural proteins tend to remain in just one conformation — but it seems clear that protein machinery has mastered a fine balance. Functional proteins are flexible enough to move between conformations at body temperature, but rigid enough to possess just a few stable states. What are the factors that determine this delicate compromise between structure and dynamics?

In real proteins, this question is probably intimately connected to protein solvation. Now Jayanth Banavar at Pennsylvania State University and his co-workers have adduced some more general considerations that seem necessary for conformational switching of chain-like molecules, which they argue amount to a set of 'design principles' for nanomachines (*Proc. Natl Acad. Sci. USA* **106,** 6900–6903; 2009).

A chain of simple hard spheres will, if warm enough, adopt a plethora of random-coil configurations, all more or less likely. You won't get a machine from that. And if the spheres interact to promote compaction, they may collapse into one of many equivalent close-packed configurations, again with no prospect of functionality. The ideal is an intermediate state in which there are just a few stable conformations and relatively labile transitions between them. Banavar and colleagues draw the analogy of liquid-crystal bulk phases, the switchability of which itself provides technological functionality.

They say that two factors are sufficient to 'thin out' the stable structures of the chains. One, familiar from liquid crystals, is anisotropy, which is in fact already inherent in a chain of monomers merely because the chain axis breaks spherical symmetry. In real amino acids, of course, the anisotropy is stronger than that. The other factor is coupling between monomers, from steric avoidance or hydrogen bonding, say. This coupling means that local coordinate frames of each monomer can't be defined independently of one another.

In simulations, these two features are enough to generate distinct intermediate conformations (helical and saddle-like) between the highly degenerate compact and random-coil states even in rather short chains, just as anisotropy opens up liquid-crystal phases between the bulk solid and liquid. Moreover, these intermediates can be switched thermally, but not too rapidly.

In this view, it may be wrong to insist that there is anything 'special' about proteins: they are specific examples of a generic phase of molecules that, poised between dense, deathly order and unstructured chaos, makes life possible. This adds to the (old) notion that it is in the 'exotic' fluid phases, such as liquid crystals and glasses, that we will find intimations of life-like behaviour. ❐