The group synthesized gold and silver nanoparticles in the 2–100 nm size range and decorated their surfaces with Herceptin — a drug that binds to ErbB2 receptors found on breast cancer cells. They found that the uptake of these nanoparticles by the cells was size-dependent, in harmony with previous data^{3,4}. They further showed that particle geometry, including size and curvature, may enhance binding of Herceptin to the receptors and cause internalization of the nanoparticle–receptor complex. Their crucial observation was that the depletion of the ErbB2 receptors from the cell membrane owing to this internalization directly influenced the biological activity of the cell. Most importantly, specific cell-growth pathways were inhibited and programmed cell death (apoptosis) was enhanced, particularly for particles in the 40–50 nm range (Fig. 1).

This closed the loop, demonstrating the first evidence of nanosize-based control of basic molecular pathways that can be potentially used for cancer treatment. What appears to be on the horizon is the

use of nanoparticles as drugs — as truly active ‘nanomedicines’ as opposed to their current role as passive nanocarriers. New insights for understanding size-based toxicities for medical and industrial nanoparticulates may also emerge from these considerations.

The cellular uptake of nanoparticles surely depends on size^{5,6} and is greatly impacted by the shape^{7,8} and the physico-chemical properties of the nanoparticles. Disc-like, cylindrical and hemispherical particles substantially outperform spherical particles when it comes to evading uptake by phagocytic cells, flowing through capillaries and firmly adhering to the walls of blood vessels. With many new protocols for making nano- and microparticles of different shapes and sizes^{9,10}, we envisage that new classes of cancer therapeutic agents that act by virtue of their size will soon emerge.

The development of a successful nanoengineered intravascular therapeutic agent needs to accomplish four major tasks: to navigate in the bloodstream (Fig. 1a); evade biological barriers (Fig. 1b);

localize in a site- and cell-specific manner (Figs 1a,c); and exquisitely target the biological pathways for the pathology being treated (Fig. 1d). The importance of nanoparticle size and shape with respect to the first three has been established in the literature. The work by Chan and colleagues creates a new fundamental perspective on the fourth, and clarifies the importance of geometry in cell uptake. All four of these tasks are necessary. What is needed next is a nanoengineered system that can perform all of them. The race is now officially open.

References

1. Jiang, W., Kim, B. Y. S., Rutka, J. T. & Chan, W. C. W. *Nature Nanotech.* **3**, 145–150 (2008).
2. Matsumura Y. & Maeda H. *Cancer Res.* **6**, 6397–6392 (1986).
3. Osaki, F., Kanamori, T., Sando, S., Sera, T. & Aoyama, Y. *J. Am. Chem. Soc.* **126**, 6520–6521 (2004).
4. Chithrani, B. D., Ghazani, A. A. & Chan, W. C. W. *Nano Lett.* **6**, 662–668 (2006).
5. Gao H. et al. *Proc. Natl. Acad. Sci. USA* **102**, 9469–9474 (2005).
6. Decuzzi P. & Ferrari M., *Biomaterials* **28**, 2915–2922 (2007).
7. Champion, J. A. & Mitragotri, S. *Proc. Natl. Acad. Sci. USA* **103**, 4930–4934 (2006).
8. Geng, Y. et al. *Nature Nanotech.* **2**, 249–255 (2007).
9. Rolland, J. P. et al. *J. Am. Chem. Soc.* **127**, 10096–100100 (2005).
10. Champion, J. A., Katare, Y. K. & Mitragotri, S. *Proc. Natl. Acad. Sci. USA* **104**, 11901–11904 (2007).

SELF ASSEMBLY

Design by DNA

Most self-assembly techniques rely on the chemistry and charge of the building blocks involved, which can make it difficult to control the properties of the final structure. It has been known for a decade that if DNA strands are attached to nanoparticles, they can direct the self-assembly process, with the properties of the DNA rather than those of the nanoparticles determining the final architecture. However, the full potential of this approach has not been exploited.

Now, two groups of researchers have demonstrated the power of the DNA-guided approach by showing how gold nanoparticles can be made to self-assemble into different crystal structures, with the details of the structures depending on the properties of the DNA strands.

Oleg Gang and co-workers at the Brookhaven National Laboratory (*Nature* **451**, 549–552; 2008) and Chad Mirkin and colleagues at Northwestern University and the

Argonne National Laboratory (*Nature* **451**, 553–556; 2008) used similar methods in which the free end of the DNA was a single-stranded ‘linker’ region. This linker directs the self assembly by binding to a complementary linker region attached to another nanoparticle. If each nanoparticle has multiple strands attached, they can bind in many directions to form a three-dimensional structure.

Mirkin and colleagues used small-angle X-ray scattering to show that a face-centred-cubic crystal structure (left) was formed when a self-complementary linker was used, whereas a combination of two different linkers that were complementary to each other resulted in a body-centred-cubic structure (right). The length of the DNA could also be varied to give different interparticle distances, although both groups concluded that longer, more flexible strands gave the best crystallinity with high long-range order. If the strands were too short and rigid, amorphous structures were produced.

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