Jocelyn H. Ng
IMI Consulting GmbH
Auf dem Amtshof 3
30938 Burgwedel, Germany

Leodevico L. Ilag
Xerion Pharmaceuticals AG
Sauerbruchstrasse 50
81377 Munich, Germany

The dangers of generalization in nanotechnology

In a recent article in *Drug Discovery Today*, Sahoo and Labhasetwar [1] provided a highly optimistic account of the potential of nanotechnology in drug delivery and in diagnosis. One of the dangers of such a review, or 'preview', of nano-sized carrier systems is that a wide range of systems are considered as if they all behave similarly. Some nanotechnology approaches will work and some will not. The authors have, rightfully, selected data from a wide variety of literature sources, which generally illustrate the advantages of nanosystems; this technology thus appears to be solely beneficial. Readers should be reminded that many were working in the field before the modern, encompassing nomenclature was invented. It was Peter Speiser who, in the early 1970s, produced by micellar polymerisation what he quaintly termed 'nanoparts' [1]. He differentiated these nanoparts into nanoparticles and nanocapsules, and studied them as vaccine carriers. There has, therefore, been a quarter of a century for nanoparticles to be developed. Marty *et al.* discussed progress in 1978 [1], and Kreuter reviewed the topic in the same year [2].

The unifying feature of the field of pharmaceutical nanotechnology is, of course, the size range of the particles or system. The nanometer size range is, indeed, important in allowing, as the authors state, access to tissues from which larger carriers are excluded. But at the same time, extremely small size provides two features: low volumetric capacity and high surface area. Both characteristics, in fact, pose problems – a limited capacity for active compounds and the potential for instability, respectively. With dendrimers, whose maximum size will be of the order of 10 nm, the capacity of the interior is low and, unlike micellar structures with their 'liquid' interiors, dendrimers usually possess a largely inflexible branched core. Proteins often have a diameter that is equivalent to many carriers in the nanometer size range, thus, as protein carriers, the smallest nanoparticles have their limitations. Aggregation of primary nanoparticles also determines their effective particle size. Nanosized dendrimers, when added to tissue culture media, can often flocculate to an extent that is dependent on the nature and, particularly, ionic strength of the medium. Their state of aggregation *in vivo* is difficult to ascertain, but it is unlikely that they will remain in their native state in blood, tissue and organs. Hydrophilic nanosystems are more immune to such problems, but their hydrophilic nature might influence uptake adversely.

The absorption or covalent attachment of specific ligands to the surface of nanoparticles can lead to specific interactions with biological surface receptors, but these surface ligand molecules, without doubt, change the physical nature of the surface. They might, or might not, reduce the likelihood of flocculation or aggregation. What is yet to be ascertained is the optimal spacing and conformation of ligand molecules on the surface of carriers. With improved knowledge of the molecular topology of receptors, this issue could be addressed more precisely, particularly with the pre-determined chemical architecture of dendrimeric systems.

One topic that has, perhaps, been neglected is the behaviour of particles in the circulatory system. This will be determined by: i) the interaction of nanoparticles with erythrocytes and other blood components; ii) the association of primary nanoparticles with themselves and with vessel walls and; iii) the influence of elasticity, when the diameter of the system exceeds that of the capillary vessels. The last point is unlikely to be an issue with nanoparticles, unless the particles have aggregated; here, the reversibility of any such particle–component or particle–particle interactions is key. Any significant number of nanoparticles, for example in the lymphatic vessels, is likely, at least, to influence lymphatic flow. We are presently studying the flow behaviour of blood–nanoparticle and microparticle mixtures.

It is undoubtedly true that nanosystems offer the potential for enhanced delivery and targeting. The sheer variety of structures that can be built up by self-assembly or covalent attachment of components, say, of dendrimers or dendrons, offers much scope, particularly if these structures can be fabricated at will. One approach that is frequently neglected is the combination of two or more technologies, for example, the incorporation of nanosystems within other carriers, such as emulsions and liposomes.

There is a general issue centred around the enhanced permeation and retention effect in targeting and diagnostic systems. The criteria for success in drug targeting are much more severe than those for diagnostic success, where, essentially, only an enhancement of signal over background is required. In treatment, if there is to be true success, accumulation at the target site should, ideally, be complete. So far, this has not been achieved – the balance of drug concentration has only been shifted moderately in favour of the target.

The potential of nanosystems to cause adverse effects needs to be thoroughly investigated, as size partly determines organ distribution.

Fascinating phenomena are reported with nanoparticles: polysorbate 80-coated nanoparticulates have been shown to penetrate the blood–brain barrier [3], but this can not yet be generalized. If this was the case, then it

 1359-6446/04/$ – see front matter PII: S1359-6446(03)02934-9

would, in fact, pose serious problems with regards to toxicity.

The safety of macro- or micro-sized particles of the same materials does not necessarily translate into the safety of nanomaterials. Early work by Casley-Smith [4] demonstrated the widespread distribution of particles in the body, thus highlighting the tracking of systems as an essential consideration during early clinical studies.

At the extreme, of course, systems with diameters of the order of 5–10 nm, are at a boundary between the molecular and the particulate state. This is especially true with dendrimers; therefore, the question posed is, at what point does a system become particulate?

Of particular interest to my group is the fate of nanosystems after oral administration. Nanoparticles can be absorbed via M cells of the gut-associated lymphoid tissues, albeit in low amounts, if they have hydrophobic exteriors. There are both beneficial and adverse possibilities as a result [5]. It is the gradual piecing together of information about the fate of these particles that will lead to a better understanding of the relationships between nanoparticle diameter, surface character, interactions and transport, leading to the optimal choice of systems for therapy and diagnosis.

Ultimately, the principal challenge with nanoparticles containing active agents is to design systems that protect the active from degradation, but enable it to be released at the appropriate site at the appropriate rate; but, even then, the release of a drug from a carrier at the site of action does not necessarily, or always, lead to lower systemic levels [6] because free drug is just that – it can freely diffuse.

We must ensure that, as pharmaceutical scientists, we do not inadvertently add to the hype surrounding nanotechnology.

References

1 Marty, J.J. *et al.* (1978) Nanoparticles – a new colloidal drug delivery system. *Pharm. Acta. Helv.* 53, 17–23

2 Kreuter, J. (1978) Nanoparticles and nanocapsules – new dosage forms in the nanometer size range. *Pharm. Acta. Helv.* 53, 33–39

3 Alyaudtin, R.N, *et al.* (2001) Interaction of poly(butylcyanoacrylate) nanoparticles with the blood-brain barrier *in vivo* and *in vitro*. *J. Drug Targeting* 9, 209–221

4 Casley-Smith, Jr (1964) An electron microscopic study of injured and abnormally permeable lympatics. *Ann. New York Acad. Sci.* 116, 803–30

5 Hussain, N. *et al.* (2001) Recent advances in the understanding of uptake of microparticulates across the gastrointestinal lympathics. *Adv. Drug Deliv. Rev.* 50, 107–142

6 Willmott, N. *et al.* (1985) Adriamycin-loaded albumin microspheres: preparation, *in vivo* distribution and release in the rat. *Biopharm. Drug Dispos.* 6, 91–104

A. T. Florence
Centre for Drug Delivery Research
The School of Pharmacy
University of London
29–39 Brunswick Square, London
WC1N 1AX UK

Advancing applications of microarrays

Malcom G. Pluskal, Consulting Services, Acton, MA, USA and **Jutta Bachmann**, Bachmann Consulting, Hagelundveien 44, 1450 Nesoddtangen, Norway and Project Manager of BioChipNet.de, operated by the NMI Natural and Medical Sciences Institute at the University of Tübingen, Markwiesenstr. 55, 72770 Reutlingen, Germany, e-mail: info@jutta-bachmann.com

This year, *Chips to Hits* (October 28–31, 2002) moved to Boston and attracted an audience of ~1600 delegates and 90 exhibitors, discussing latest developments and applications within the field of microarray and biochip technologies. The conference, itself, has morphed over the years from a purely technology-driven discussion into an applications-oriented forum, which continues to seek out emerging technologies. It has provided a valuable forum for both developers and users of microarrays to present their latest developments and applications.

Innovations in tools and methods

The extremely popular pre-conference workshop, 'Innovations in tools and methods for clinical and biomedical applications', provided an excellent basis for the discussion on the needs and demands of microarray technology. This session was opened by Guido Grandi of Chiron Vaccines (http://www.chiron.com), who discussed the application of microarrays in vaccine development. Sanford Simon of Rockefeller University (http://www.rockefeller.edu) provided an insight into approaches using luminescent quantum dots to label live cells and their use in the long-term imaging of living cells. Christian Hennig of Genovoxx GmbH (http://www.genovoxx.de) gave an outline of massive paralleled single-molecule sequencing, which was followed by an intriguing insight into a carbohydrate-based microarray technology, presented by Denong Wang of Columbia University (http://www.columbia.edu). The session closed with a presentation by Cleo Salisbury of the University of California (http://www.ucla.edu) on how substrate specificity of a protease can help in the design of potent and selective substrates and inhibitors.

1359-6446/04/$ – see front matter PII: S1359-6446(03)02958-1