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Editorial commentary

Pharmaceutical nanotechnology: More than size Ten topics for research

The Pharmaceutical Nanotechnology section of the *International Journal of Pharmaceutics* came into being in recognition of the increasing number of papers which addressed the preparation and evaluation of nanocarrier systems (Florence, 2004; Rytting, 2004). The section has given a more distinctive profile to this research, maintaining the core pharmaceutical elements of endeavours in the field. Since the inception of the section over 250 papers have been published covering a wide range of topics. We are naturally pleased with the progress made and we would like to encourage more submissions which speak to the many pharmaceutical and biopharmaceutical issues in nanotechnology.

However, it is timely to reflect on the subject. We receive many papers on the preparation and *in vitro* evaluation of nanosystems, but perhaps too few which examine the difficult field of targeting nanosystems to biological targets, there to deliver therapeutic agents in sufficient quantities and at a rate which will produce beneficial results. Much fewer are the papers which admit to difficulties in the task of nanoparticle targeting. These, however, are necessary if we are to interrogate the real question of why targeting has not so far fulfilled its expectations, and if we are as a result to formulate research which will confront these issues.

What follows are a few personal suggestions for topics for examination, research, determination or study and, ultimately for publication, we hope in *IJP*.

1. *The relevance to the whole animal of in vitro tests of activity, selectivity, uptake and toxicity of nanoparticulate carrier systems*.

   In vitro systems are generally static whereas most interactions between particles and ligands on cell surfaces occur under dynamic conditions. Flow of blood in which nanosystems move generally decreases the interaction between carrier and target and the facts of laminar and non-laminar flow in vessels and other tubules is determined by the velocity and velocity gradients in blood vessels (Florence, 2006).
2. *Scaling factors in animal models and the extrapolation of results to human subjects*.

   The relevance of animal studies which form the greatest number of sources of biodata is unclear. Does a 100 nm particle behave the same way in a mouse and in a human? What is the importance of the distance travelled between point of entry to point of interaction with target? How does the physiology of various species influence interpretation of data? Kararli (1995) reviewed aspects of the physiological differences in relation to drug absorption between experimental animals and humans. A similar exercise is necessary to determine the influence of species differences in nanocarrier behaviour and fate.
3. *The causes of the differential uptake and transport of particles in different cell lines in vitro and tissues in vivo*.

   Studies of transfection of a variety of cell lines with a particular DNA-complexing agent have frequently shown very marked differences in effectiveness. For example, in the case of dendriplexes (dendrimer–DNA complexes), Bayele et al. (2005) have shown 1000-fold differences in transfection. Is this due to cell size, membrane differences, cell culture media, differences in cell division rate or the nature of the nucleus and cytoplasm?
4. *The influence of the nature of the polymer or other construction material in the manufacture of nanosystems on their biological and colloidal behaviour*.

   There has been significant concentration on the effect of the size of nanoparticles on physical and biological behaviour but perhaps less on the nature of the polymer in as far as this affects the capacity of the system for encapsulation of therapeutic agents, particle flocculation and interaction at close approach of nanoparticles and surface receptors.
5. *Analysis of the colloidal behaviour of nanoparticles and especially the influence of surface ligands on this behaviour*.

   Is one of the reasons why addition of specific ligands to the surface of nanoparticles, whether by covalent attachment or by adsorption does not always lead to improved targeting in animals, the way in which the ligands affect the stability of the nanosystems?
6. *Nanoparticle navigation in complex biological networks*.

   A better understanding of the movement of nanoparticles in the complex environment in which they are deposited, in tissues, in tumours and in blood and lymph is essential for prediction of behaviour. The influence of particle size, shape

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and flexibility on such movement is key (Geng et al., 2007). Does shape matter? If flow matters then asymmetric flow is clearly different from the flow of spherical particles, hence there is a need for better comprehension of such behaviour.

7. *Analysis of published data to move the subject towards greater predictability of nanoparticle behaviour*.

   Targeting activity is essential in the design of many delivery systems, vaccines and gene delivery vectors, hence the importance of collating the already voluminous material which has been published and finding common threads to improve, again, predictability.

8. *Pharmaceutical aspects of nanotoxicology or nanosafety*.

   It is clear that we must have more specific information on the safety of nanosystems, and the influence of the nature of their surfaces and the material of which they are composed, their porosity, size and shape elucidated.

9. *Pharmacokinetics of drugs and other agents encapsulated in nanosystems*.

   A fairly self-evident need.

10. *The physical chemistry of peptide, protein or macromolecule—polymer miscibility in relation to incorporation of these molecules in polymer nanoparticle, their stability and release*.

    In the biological quest the pharmaceutical and physicochemical issues in formulation must not be under-estimated. One lack seems to be a systematic study of the interactions between peptide and proteins and DNA with the variety of polymers used in the construction of nanosystems. The basic thermodynamics of mixing under the conditions of preparation will yield valuable data.

The above 10 topics are possibly an idiosyncratic and certainly an incomplete list of topics. They arise from my own interests in pharmaceutical nanotechnology, driven also by the need to counteract the exaggerated claims for nanosystems in drug delivery and targeting by addressing the core factors which prevent quantitative delivery of therapeutic agents to complex targets such as tumours and sites of inflammation. Perhaps it is now time also to examine again, theoretically, the enhanced permeation and retention (EPR) effect and other phenomena such as extravasation. The existence of fenestrations in blood vessels does not automatically mean that particles of a diameter less than the "pore" size can pass through them. Some phenomena are extremely difficult, if not impossible at present, to investigate *in vivo*, hence there needs to be a theoretical approach to many of the phenomena we invoke to explain delivery and targeting with nanoparticles. The stochastic nature of many interactions must be incorporated into predictions. And while we are studying the biological barriers to targeting we must devise new systems which are better able to take their load quantitatively to their targets yet release them in a predictable manner when they reach the site of action.

We hope to see such issues addressed in papers submitted to us.

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