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Preface

This is the second Special Issue of *International Journal of Therapeutics* to arise from a meeting of the GTRV (Groupe Thématique de Recherche sur la Vectorisation). The GTRV is a mainly French-speaking special interest group bringing together scientists form the public and private sectors interested in carrier systems or their targets. Carriers are defined as any system that could modify the distribution of a biologically interesting molecule at the tissue, cellular or sub cellular level *in vivo* or *ex vivo*. This covers not only drug delivery and diagnostics but also techniques used in experimental cell biology. The wide range of technology which can be employed towards these ends is illustrated by the range of articles in this Special Issue, describing work first presented at the group's annual meeting in Angers (France) in December 2008.

We have entitled this Special Issue "Challenges for Nanotechology in Delivery and Imaging". The development of new drug entities and methodology for non-invasive imaging brings with it the need for effective carrier systems to allow their full potential to be realized. Nanosized particles can be used as carriers for therapeutic molecules, as contrast agents and as imaging agents in their own right (and can sometimes combine these functions). The review from the group of Jean-Pierre Benoît describes a versatile type of colloidal carrier: lipid nanocapsules. These small particles, with a diameter low enough to allow extravasation through tumour endothelium, can be loaded with a range of water-insoluble drugs and have particular applications for cancer chemotherapy. Their surface properties can be easily modified by the inclusion of different surfactants, for example, to give "Stealth" properties.

A recent therapeutic innovation is the use of nucleic acids, and in particular small interfering RNA (siRNA). However, these fragile, water-soluble molecules need innovative delivery systems and this is the subject of the mini review by Michael Keller.

One developing area of nanotechnology research is the design of carrier systems that can self-assemble in aqueous solution, removing the need for organic solvents. One such system is the block copolymer micelles described by Boudier et al. These systems are pH-sensitive and could be used to release active compounds within endosomes. Another auto-associative system can be formed from cyclodextrin- and dextran-based polymers. Othman et al., have used state-of-the art characterization techniques, including isothermal titration calorimetry, to probe the structure of such systems loaded with gadolinium for magnetic resonance imaging. Another, more traditional, carrier system in the form of poly (lactide-*co*-glycolide) nanoparticles loaded with copper complexes for a similar application has been developed by Courant et al.

The oral route has obvious advantages for safety and patient compliance, thus a number of contributions to this Special Issue address the question of improving bioavailability by this route. One strategy is to prepare prodrugs of poorly absorbed molecules that can be handled by the lymphatic pathway. Lalanne et al. have prepared glycerophospholipidic prodrugs of an antiviral agent: didanosine. Obviously, it is important that the active molecule can be released under appropriate conditions, so a detailed study of prodrug metabolism was performed, leading to the conclusion that a phosphorylated derivative was cleaved more rapidly than a non-phosphorylated one. The release of active didanosine triphosphate within HIV-infected cells was also demonstrated. Low solubility in intestinal conditions is another cause of poor oral bioavailability and cyclodextrins can be useful additives in this respect. Marçon et al. prepared an oral formulation of the pre anaesthetic midazolam in this way.

The presence of non-absorbed antibiotics in the colon after oral antibiotherapy leads to the selection of antibiotic-resistant microbial strains. An ingenious solution is proposed by Khoder et al. in the form of zinc pectinate beads containing activated charcoal which is released by the colonic flora and can adsorb antibiotics such as ciprofloxacin. The stability of any drug delivery system in the gastrointestinal environment is an essential feature for its performance. Roger et al. have studied the stability of the lipid nanocapsules referred to above in various simulated media, with emphasis on the difference between the fed and fasted state.

The use of nanocapsules by the intravenous route also implies quality control procedures. Hureaux et al. describe how they ensured that lipid nanocapsules can be prepared free of genetically modified organisms (by the choice of surfactant) and that they do not modify the acid–base balance in blood. They also optimized freezing protocols in liquid nitrogen. A meeting in France would not be complete without reference to the French paradox, and Barras et al. have optimized the encapsulation of two anti-oxidant polyphenols of plant origin in these same lipid nanocapsules to facilitate their pharmacological usage.

The passage of biological barriers is an on-going concern in the GTRV. Wasungu et al. opted for a physical approach: electroporation, and use a three-dimensional spheroid model to study the mechanisms. The blood–brain barrier is one of the major challenges for drug delivery, and Chang et al. show in this issue that receptor-mediated endocytosis of nanoparticles is a promising strategy. The following article also addresses the question of specific targeting, this time with sugar moieties directed towards hepatocytes with the aim of developing non-viral gene carriers (Morille et al.).

Carbohydrate-mediated targeting to the liver is also the aim of the work of Richard et al., in this case with amphiphilic perfluoroalkyl chelating agents destined for functional scintigraphic

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imaging of the liver. In a similar vein, Sancey et al. demonstrate how optical imaging can be used to optimize drug development in oncology.

The most important test for any nanotechnology is whether it can produce results in a relevant *in vivo* model. Allard et al. report the cytotoxic effect of ferrocifen, a bioorganic compound, encapsulated in lipid nanocapsules in both ectopic and orthotopic 9L-glioma in the rat. Finally, continuing the cancer treatment theme, a short communication by Benyettou et al. on the association of a bisphosphonate with maghemite nanocrystals shows that magnetic targeting with iron oxide nanoparticles is an interesting approach.

The contributions to this Special Issue demonstrate the wide range of delivery strategies which can be proposed for both existing and new drugs. They illustrate the importance of thorough characterization of systems and of careful evaluation, both *in vitro* and *in vivo*, with imaging playing an important role in the latter. Progress is definitely being made in the field, and the GTRV is proud to be part of it.

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