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Cover Story

Pharmaceutical nanotechnology: Unmet needs in drug delivery

Nanotechnology has been gaining interest within and outside the scientific community. Conferences addressing different aspects of this rapidly growing field are organized at many different places. In May 2009 the LTS Academy organized a two-day workshop to discuss the relevance of nanotechnology to the drug delivery field. The LTS (Lohman Therapeutic Systems) Academy is an independent forum of scientists discussing timely topics in the field of drug delivery. The questions on the table related to the identification of unmet needs in the drug delivery field and possible nanotechnological solutions. The workshop was translational in different ways. Speakers were chosen from academia and industry, each of them covering a specific approach to address unmet needs in drug delivery. And their background ranged from clinical to electrical engineering. Multidisciplinary and translational, indeed!

The traditional definition of nanotechnology speaks of 'control of matter'. Many newly developed nanomedicines (e.g., targeted liposomes, polyplexes, nanotubes, modified/artificial viruses) can be designed to serve specific therapeutic purposes. Physicists, biologists, chemists, informatics experts, physicians, and pharmaceutical scientists all play a role in developing these 'smart' technologies for targeted delivery, for bio-imaging or for the development of new devices. In this context, as the first speaker (Daan Crommelin) proposed, the descriptor 'smart' technologies may be better than 'nanotechnologies', as in many cases the end product is in the micrometer range or larger and the feature that is of critical importance stands out not because of size but because of function. The speakers that followed indeed showed how smart these new nanotechnological approaches can be.

The notion that the era of nanomedicines started in the previous century is demonstrated when looking at the development of nanocrystal technology, discussed by Eugene Cooper. Rather simple wet milling techniques led to a decrease of the crystal size down to the hundred nanometer range. These dispersions are stabilized with surface active polymers. The oral bioavailability of nanocrystal based formulations of poorly water-soluble drugs has been clearly enhanced for some drugs. Poorly water-soluble nanocrystals were also used for parenteral injection of imaging material for CT scans. The 'nanocrystal story' clearly shows that rather simple techniques can improve the performance of poorly water-soluble drugs dramatically, although the number of such drugs that are marketed is limited at this point.

Nanosized materials are special, but they obey largely known physicochemical principles in terms of interactions with surfaces, diffusion behavior and hydrodynamics. When developing new therapeutic and diagnostic systems on the basis of new nanomaterials, these principles apply and should be recognized. The anatomical and physiological barriers these nanoparticles have to overcome to perform efficiently in terms of therapeutic effect or imaging power, still offer many mysteries, emphasizing the complexity of the task and our limited understanding at present. With a better understanding of these complex systems, according to Sandy Florence, modeling approaches would win in predictive power and assist in rational design.

Present drug release systems suffer from a number of disadvantages. Pay load may be low, burst release often goes together with incomplete release of the drug and poor scalability of the manufacturing process. A novel, easily upscalable nanofabrication method based on hydrogel templates, described by Kinam Park, can provide microstructures with high drug load capacity, no burst effect and controllable release characteristics. This is a clear example of introducing technologies developed in other fields of expertise into the pharmaceutical sciences.

New nanomaterials such as carbon nanotubes may offer new opportunities for targeted drug delivery. Kostas Kostarelos posed the key questions. How do they interact with cells and how do they behave in vivo? Are there new mechanisms by which they are taken up? Using electron microscopy, carbon nanotubes have been observed in vitro penetrating cell outer cell membranes by piercing through them with their 'sharp' ends. And the first evidence has been published describing penetration of the lining of the endothelium in the kidney. In vivo disposition of these carbon nanotubes is under investigation. An attempt was made to combine two new chemical compound families (carbon nanotubes and dendrimers) to optimize carrier characteristics: modifying carbon nanotubes with positively charged dendrimers may make them excellent carriers for siRNA molecules.

Imaging techniques enjoy a growing interest in nanomedicines. More and more powerful magnetic fields increase the resolution of MRI imaging. Other non-invasive imaging techniques like CT X ray analysis, radio-scintigraphy and PET provide us with information regarding optimum treatment protocols as well. These were areas covered by Ick-Chan Kwon. Nanosized particles can assist in improving their performance. For instance, superparamagnetic iron oxide nanoparticles are being used as tissue specific contrast agents. What other options are there? New fluorescent probes can be incorporated in 'smart' polymer-based delivery systems. Examples are (peptide/protein)-targeted polymers conjugated with quenched fluorescent probes which are 'activated' after tissue specific cleavage. These systems can be used for monitoring angiogenesis or apoptosis. Last but not least, the concept of targeted tissue or cell imaging can be taken a step further by incorporating a therapeutic molecule into the polymer-based complex: targeting efficiency is monitored and directly coupled to the desired therapeutic effect.

Mauro Ferrari addressed the question how size and shape affect flow behavior, cell interaction and biodegradability. Modeling fluidics shows that for nanosized particles margination dynamics draw particles to the wall of a blood vessel. The shape of the particles is of great importance, confirming observations made with carbon nanotubes as mentioned

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above. Interestingly, large surface, nanoporous silicon particles show linear release kinetics because of non-Fickian diffusion and biodegradable characteristics, a characteristic not shown by larger silicon particles.

Nanotechnology must not automatically be considered to be superior to microtechnology in drug delivery. Nanocomponents may form part of larger devices, as Ron Siegel explained, with special references to improving insulin delivery for diabetic patients. Nanotechnology is part of the glucose-sensor/insulin-supply system: part of a 'smart' sophisticated multicomponent system where lithographic–electronic–polymeric–mechanical expertise is brought together to build an artificial beta-cell.

The skin is an organ where different nanotechnological approaches are being tested, which Gregor Cevc reviewed. Microneedles with different shapes and sizes, hollow or solid, biodegradable or non-biodegradable attract a lot of attention. In the case of ballistic injection systems, nanometer sized hard or soft (droplets) material is shot into the skin for intradermal delivery. This concept is now in an industrial development phase for delivery of insulin or vaccines. Skin humidity is considered one of the many factors that cause the high variability of the results. The idea of using nanoemulsions or transformable lipid vesicles for short-lasting skin penetration through aqueous pores has been subject of a long and fierce controversy both regarding the efficacy and the physical mechanisms involved. Clinical studies show effectiveness for local analgesics and, bit by bit, the driving forces are being revealed.

Viruses, and in particular lytic adenoviruses, are excellent nanometer sized potential killers of tumor cells. But their pharmacokinetic profile does not often allow efficient disposition in tumors, metastases included, as pointed out to the meeting by Len Seymour. Erythrocytes and anti-adenoviral antibodies interfere with the delivery of adenovirus to and in tumors through the EPR (enhanced permeability and retention effect). A combination of polymeric modification of the coat of the adenovirus provides efficient 'stealth' effects. Long circulation times allow the modified adenoviruses to fully utilize the EPR access route. Dendrimers, a spherical or quasi-spherical synthetic polymer family regularly used by nanotechnologists, were among the prime candidate polymers for viral coatings.

A fast growing field, partly overlapping with nanomedicines is the field of synthetic biology, which has its roots in basic research to the origin of life. Synthetic biology is defined as (i) the design and construction of new biological parts, devices and systems, and (ii) the re-design of existing natural biological systems for useful purposes. This was the emerging field described by Enrico Mastrobattista. Artificial bacteria and artificial viruses are prime examples of synthetic biological approaches leading to smart nanomedicines. Using large nucleotide libraries and combinatorial approaches, artificial bacteria with optimum characteristics for use in vaccines can be selected. The same holds for artificial virus development for specific and efficient transfection of target cells.

Like most technologies used in medicine, nanotechnological products may have a less favorable side. There are concerns about safety, both for workers (occupational hazards/exposure), the public in general or patients as a subgroup, who are exposed in the environment or in a therapeutic setting to nanomaterials. Pulmonary disposition is often seen as a major point of concern as these large surface area particles may lead to inflammatory reactions or even tumor formation. In the EU and USA legislation is under development on the handling of hazards/exposure and the need for risk assessment and risk management of nanomaterials. But the point made by Paul Borm and other speakers was that it is impossible to generalize: each material has to be taken on its own merits. Size, shape and morphology play a key role in determining safety.

In conclusion, this conference clearly demonstrated that nanomedicines provide exciting opportunities to improve our arsenal of treatment tools. Translational, cross-cutting and, above all, 'smart' approaches are essential to be successful in the clinic. Different disciplinary experts ranging from physicist to physician and toxicologist should be involved in the thought processes and ensuing actions to fully exploit the potentials of nanomedicines.

It was a great occasion to have these international experts together at this meeting and we, as organizing committee, are pleased that many participants put their thoughts on paper and contributed to this special issue on Nanotechnology of the Journal of Controlled Release.

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