



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>

Contents lists available at [SciVerse ScienceDirect](http://www.sciencedirect.com)

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Cover Story

Toxicity risk of nanocarriers

Over the last few decades, there has been ever-increasing research interest in nanotechnology applications in the drug delivery and biomedical fields. Many researchers in industry and academia are developing new nanoparticles with various materials, structures and properties. Nanoparticles have been routinely tried for developing more sensitive diagnostics, improved tissue engineering scaffolds, and enhanced targeted drug delivery systems. Nanoparticles have also been used in items that we face in our daily lives, such as in cosmetics, foods, and fabrics. The ubiquitous and ever growing presence of nanoparticles requires careful consideration of their potential effects on our body and environment.

In the beginning of the nanotechnology fever, unrealistic hopes were placed on the unproven potential of nanosystems. In the drug delivery field, numerous nanoparticle formulations have been used to increase the drug delivery at the target site, especially the tumor tissue. It is true that the nanoparticles deliver more drugs to the target tumor tissue, and the increase in drug delivery ranges from 2 to 40 folds over the control formulation. This, however, should be taken with caution. Even for the nanoparticle formulation that delivers 40-fold more than the control, the total amount delivered to the target tissue is still only about 5% of the injected dose. Simply put, more than 90% of the injected dose goes to other normal tissues and organs. Apparently, nanoparticles are far from the expected “magic bullet.” More importantly, the unspecific, or uncontrolled, biodistribution of nanoparticles still affects the normal cells, causing a variety of serious side effects associated with chemotherapy. The potential benefit of nanoparticle based targeted drug delivery still remains just potential.

Because the vast majority of the injected nanoparticles are still accumulated in the normal tissues, the risks of using nanoparticle formulations need to be considered carefully. The nanoparticles have very different physicochemical and biological properties as compared with conventional low molecular weight drug molecules, influencing the blood circulation and biodistribution, and thus, pharmacokinetic and pharmacodynamic characteristics. The cumulating data also suggest that the biodistribution of nanoparticles depends on the particle size and shape. Due to a variety of different structures it is rather difficult to make any generalized conclusions on the nanoparticle toxicities. Rather, the toxicological effects of nanoparticles need to be analyzed depending on the context of their use, i.e., the route of administration, dose, residence time in the body, material size, and material interaction with the body. The biodistribution of the nanoparticles has been studied mainly as a part of the targeted

drug delivery, and it is well known that the majority of the administered nanoparticles are cumulated in the liver, lung, spleen, and kidneys [1,2]. One important, but frequently neglected, organ is the ovary.

In an article in this issue, Professor Karsten Mäder and his team in cooperation with Dr. Thomas Mueller's group studied the toxicity risk of nanocarriers in the ovary. They detected a high local accumulation of different nanocarrier systems (nanoparticles, nanocapsules and nanoscaled lipid emulsion) in specific locations of rodent ovaries [3]. The nanocarriers were loaded with a near infrared (NIR) fluorescent dye. The *in vivo* distribution of the respective nanocarrier system was characterized after intravenous administration into mice by multispectral NIR fluorescence imaging. This imaging technique allowed a non-invasive monitoring of the ovaries over several days and confirmed the accumulation in the ovaries for all nanocarriers. *Ex vivo* studies were followed to examine the local ovarian accumulation characteristics. The obtained *in vivo* and *ex vivo* fluorescence imaging results were further combined with confocal laser scanning microscopy images. The impact of particle size on accumulation in the ovaries was further investigated using PEG-PLA block polymers synthesized by Professor Achim Göpferich and his team. The PEG-PLA block copolymers were used to produce different nanoparticle batches varying only in size. The results showed that all nanocarrier systems accumulated partially in the ovaries of different mouse species and also of Wistar rats. Within the ovaries, the accumulation was limited to localized specific structures. The accumulation in the ovaries was found to be size-dependent. Nanocarriers ≤ 35 nm in diameter were not accumulated in the ovaries, while those between 45 and 350 nm were accumulated in significant amounts. In this size range the bigger particles seem to be accumulated more than the smaller ones.

The work by Professor Karsten Mäder and his colleagues presents a few important observations. First, the higher accumulation of the larger particles in the ovaries indicates that it is preferable to use smaller particles, if possible, to reduce the unwanted accumulation in the ovaries. Second, it underlines that *in vitro* cell toxicity study alone is inadequate in full characterization of the potential toxicity of the nanocarrier drug delivery system. Third, it emphasizes the importance and need of early and comprehensive *in vivo* studies in pharmaceutical research. While the results obtained in small animals may be still preliminary, they highlight the importance of potential toxicity in the human ovaries. At the same time, however, the information opens up a new avenue of ovarian targeted therapies.

References

- [1] P. Ruenaroengsak, J.M. Cook, A.T. Florence, Nanosystem drug targeting: facing up to complex realities, *J. Control. Release* 141 (2010) 265–276.
- [2] A.M. Nyström, B. Fadeel, Safety assessment of nanomaterials: implications for nanomedicine, *J. Control. Release*, doi <http://dx.doi.org/10.1016/j.jconrel.2012.01.027>.
- [3] A. Schädlich, S. Hoffmann, T. Mueller, H. Caysa, C. Rose, A. Göpferich, J. Li, J. Kuntsche, K. Mäder, Accumulation of nanocarriers in the ovary: a neglected toxicity risk? *J. Control. Release* 160 (2012) 104–111.

Kinam Park
Purdue University
Department of Biomedical Engineering and Pharmaceutics
West Lafayette, Indiana, USA
Kyung Hee University
Department of Maxillofacial Biomedical Engineering
Seoul, Korea
E-mail address: kpark@purdue.edu