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EDITORIAL

Magnetic Nanoparticles for Biomedical Applications

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Magnetic nanoparticles (MNPs) have been produced for decades and are used in a broad variety of technical applications. Examples are as widespread as ferrofluidic seals for aeronautic or automotive applications, data storage devices for information processing, or applications in the biomedical field, some of which are discussed in this theme issue. Several comprehensive reviews of biomedical applications of MNPs have been published recently (1–12). A brief search in Medline for the topic MNPs highlights that the number of publications in the field has increased exponentially throughout the past 20 years. The diversity of the field has grown considerably and represents too broad a scope to be covered comprehensively in one theme issue.

In the current theme issue, research papers and reviews are presented that deal with MNPs in various—mostly biomedical—applications. Based on the scientific background of the guest editors, a focus of this theme issue is magnetic drug targeting, in particular magnetically guided and enhanced nucleic acid delivery, also known as magnetofection. Considerable progress in this particular field has been accomplished during the last decade (10). This focus is not intended to neglect the formidable achievements with magnetic particles in other biomedical applications, such as cell tracking and positioning, magnetic cell separation, imaging and diagnostics, theranostics, magnetic actuation of cellular functions, AC magnetic field hyperthermia, etc. Most contributions to this theme issue report on applications of magnetic particles as opposed to theoretical/physical considerations. However, several papers focus on chemical and physical topics implied in the preparation and imaging/detection of MNPs as well as on mathematical models to better understand the physics of magnetofection. This theme issue provides both an overview and deeper insight into selected topics of the rapidly evolving field of biomedical applications of MNPs.

The manuscripts with biological topics focus on the enhancement of viral gene delivery as well as on the guiding of MNP-transduced cells using magnetic field gradients. Sapet *et al.* and Anton *et al.* use MNPs for enhancing adenoviral transduction and cell separation under static as well as under flow conditions. Chorny *et al*. focus on the formulation and characteristics of polylactide-based MNPs to achieve rapid MNP internalization of endothelial cells also in combination with MNP-mediated adenoviral transduction. Wenzel *et al.* and Trueck *et al.* present optimal conditions and combinations of MNPs for enhanced lentiviral transduction and local cell positioning of transduced endothelial cells. MNP loading of endothelial cells is also the major topic of MacDonald *et al.*, who give further insights into the cellular uptake process. Mannell *et al.* use MNP-loaded microbubbles that can be attracted in a magnetic field. Such microbubbles can be ruptured by ultrasound, which can be used for the local release of the cargo—in this case, a lentivirus coupled to the MNPs. Another application in this field is presented by Räthel *et al.*, who incorporate antirestenoic drugs in the magnetic microbubbles and demonstrate drug delivery to magnetizable stents upon magnetic field application. This technology could be useful for coating implanted stents with drugs. MNP-assisted gene transfer is not only applicable for the cardiovascular system. Hasenpusch *et al.* demonstrate herein a 2–3-fold higher drug accumulation and specific

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transgene expression in magnetically targeted lung regions of unanesthetized mice by applying magnetized aerosols with the long-term goal to treat localized diseases of the deeper airways. A paper on the use of MNPs for magnetic hyperthermia is contributed by Asín *et al.*, who apply alternating magnetic fields for controlled cell death of MNP-loaded dendritic cells.

Yiu *et al.* and Mykhaylyk *et al.* focus on the characteristics of MNPs. Yiu *et al.* describe multifunctional MNPs for future applications in non-invasive cell tracking, and Mykhaylyk *et al.* focus on polyethylenimine-coated MNPs to enhance viral gene delivery. Furlani and Xue present a numerical model of the magnetofection process to better understand or define key factors in order to optimize nucleic acid delivery *in vitro*. The link between such mathematical predictions and experimental results was studied by Kilgus *et al.*, who used MNPs for local positioning of MNP-loaded cells or in combination with lentiviruses for local gene targeting of cells. They also developed new magnetic tips to enhance local targeting. Importantly, their experimental outcome fits very well to the mathematical simulation. This should facilitate the use of computer simulation to further develop magnetic targeting of cells and genes.

For MNP imaging and detection, Wiekhorst *et al.* offer a perspective on magnetorelaxometry. Rümenapp *et al.* contribute a review about magnetic resonance imaging. Yigit *et al.* provide a review about the potential of MNPs for cancer diagnosis and therapy. Andriola *et al.* analyze the intercellular transfer of MNPs and show that micro-vesicles participate in the MNP release leading to MNP redistribution due to their uptake by naïve cells. This is of relevance because after *in vivo* implantation of MNP-labeled cells, a non-specific uptake by host cells may occur that has to be considered when using, e.g., MRI for analyzing the fate of transplanted cells. Finally, an interesting application of MNPs is contributed by Namiki *et al.*, who use MNPs and gradient magnetic fields for the elimination of cesium from seawater and other fluids like serum or milk. This approach is of high interest in light of the release of large amounts of radioactive material in Japan after the earthquake and tsunami in March 2011.

With this theme issue, we hope to give a detailed and up-to-date overview of the field of MNPs and their potential use in different areas of life sciences focusing on gene delivery and cell guiding, as well as to cover important aspects of physics and engineering ranging from MNP detection to magnetic gradient field design. We are very glad to have the opportunity of presenting this variety of MNP applications and would like to thank *Pharmaceutical Research*, especially Rachel Lucke for excellent editorial assistance.

INTERVIEW WITH ALEXANDER PFEIFER, KATRIN ZIMMERMANN, & CHRISTIAN PLANK

What do you think holds the key to your success as biochemists and drug delivery scientists?

Major basis are dedication and diligence. However, without the support by granting agencies and senior experts in the field, it is very hard to succeed in any scientific field. We are grateful for the support we have received so far.

What do you consider to be your key research accomplishments?

Working in academia, our most important accomplishment is the success of the students and young scientists that we teach. Apart from this, we hope that we had some major contribution to the field of magnetic targeting, viral gene transfer and pharmacology.

What was the turning point in your career?

AP: The move to pharmacology.
CP: The invention of magnetofection and the recent move to RNA therapeutics having founded ethris GmbH.

Which individuals most influenced your research career?

CP: Ernst Wagner, Max Birnstiel, Frank Szoka, Bernd Gänsbacher, and Walter Schmidt.
KZ: Jörn Piel and Alexander Pfeifer.
AP: Reinhard Fässler, Franz Hofmann, and Inder Verma.

What is the key to developing successful collaborative relationships?

Trust and mutual appreciation.

What is your philosophy of educating graduate students?

Sound technical skills, diligent experimentation, and pairing the required focus of a research plan with a view beyond the borders of their own research work. Advancing interdisciplinary research is an essential key, particularly when working with MNPs.

What is the place for collaboration with industry in academia?

Academia-industry collaboration is essential for successful translation of basic science into the clinics; this will be normally based on the scientific achievements of the academic partner and should lead to a strategic partnership.

Pharmaceutical scientists are faced with the dilemma of having to publish in biomedical or basic science journals. Does this mean cutting-edge science will not likely be featured in journals like Pharmaceutical Research*?*

These are hard times for pharmaceutical research with a decrease in new chemical entities entering the clinics/ market and pressure from other areas of life sciences. However, excellent science will prevail and will be published also in the future in this field. We do believe that cutting-edge science is and will be featured in *Pharmaceutical Research*.

Where is the field of Magnetic Nanoparticles for Biomedical Applications going? How do the articles in this theme section fill the gap?

Major advances can be expected in diagnostics (targeted MRI; review paper in this issue), theranostics (e.g. magnetic microbubbles), localized rather than systemic applications for drug targeting, magnetic cell separation combined with genetic modification of (stem) cells, magnetic cell positioning for regenerative medicine applications (Trueck *et al.*, Chorny *et al.*). Concerning disease prevention, the paper of Namiki *et al.* is an important contribution.

What are the challenges for Magnetic Nanoparticles for Biomedical Applications, and how can they be overcome?

A major challenge is the efficient magnetic targeting *in vivo*, which requires optimization not only of the MNPs and formulations of MNPs but also of the magnetic field design. There are basic limitations by physical laws. The key is keeping things simple and applying magnetic particles in applications which are realistically feasible.

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A. Pfeifer studied medicine at the Ludwig-Maximilians University (LMU) in Munich, Germany, where he also did his MD. After the approbation, he worked as post-doctoral fellow in the Institute of Pharmacology and Toxicology, Technische Universität München, Germany, where he also performed his habilitation. At the Max-Plank Institute of Biochemistry, he worked in the laboratory of Reinhard Fässler. With a Heisenberg-Fellowship of the Deutsche Forschungsgemeinschaft (DFG), he went in 1998 to the U.S. and joined the laboratory of Inder Verma at the Salk Institute in San Diego, California. At the end of 2001, he became Professor at the Department of Pharmacy, LMU Munich, Germany. In 2006, he moved to the University of Bonn, Germany, where he became the director of the Institute of Pharmacology and Toxicology. He is the founder and vice-speaker of the Pharma-Center Bonn. He is speaker of the International Graduate Research School BIOTECH-PHARMA and also mainly involved in the BMBF supported Neuroallianz. Together with Christian Plank and Bernd Fleischmann, he is heading the Research Unit "Magnetic Nanoparticle-based targeting of gene- and cell-based therapies (Nanoguide FOR917)" funded by the DFG.

K. Zimmermann studied Applied Natural Science in Freiberg, Germany, and did her PhD at the University of Bonn, Germany, at the Institute of Bioorganic Chemistry. She is now working as post-doctoral fellow in the group of A. Pfeifer at the Institute of Pharmacology and Toxicology at the University of Bonn. Together with A. Pfeifer and C. Plank she is involved in the DFG research group Nanoguide (FOR917).

C. Plank graduated in biochemistry at the University of Vienna (Austria). After a postdoctoral fellow at the University of California, San Francisco, he moved to the Technische Universität München (Germany) to become group leader and a professor at the Institute of Experimental Oncology and Therapy Research. He developed the Magnetofection^{TM} technology as well as microbubbles for magnetic field and ultrasound guided drug delivery and technologies focusing on implantable gene carriers. He is the co-founder of OZ Biosciences S.A.R.L., Marseille, France, and of ethris GmbH, Seefeld, Germany. Furthermore, he was coordinator of the EU-project "Magselectofection" and is a member in the Nanosystems Initiative Munich cluster of excellence as well as in the Munich Center of Nanoscience (CeNS), Germany.