

Magnetic Carriers Conference 2008

7th International Conference on the Scientific and Clinical Applications of Magnetic Carriers, 20–24 May 2008, Vancouver, Canada

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Beautiful Vancouver, in British Columbia, Canada, was the host location of the 7th International Conference on the Scientific and Clinical Applications of Magnetic Carriers from 20–24th May, 2008. There were over 344 delegates from 32 countries in attendance. Over the 4 days, a total of nine symposia with six invited speakers highlighted almost all the research areas in the field of magnetic particles.

The scientific program with 80 talks and 229 posters began with the opening remarks of Helen Burt (Associate Dean of Research, University of British Columbia [UBC], Vancouver, Canada) who welcomed everyone on behalf of the Faculty of Pharmaceutical Sciences and UBC. Urs Häfeli (Chairman of the meeting, UBC, Faculty of Pharmaceutical Sciences, Vancouver, Canada) then reviewed the progress in the field of magnetic carriers since the previous meeting in 2006 in Krems, Austria. Advances in the area of magnetic particles were well illustrated by the unprecedented number, 2677, of peer-reviewed publications involving magnetic nanoparticles published in 2007 alone!

The first invited speaker, Peter Zimmerman (Case Western Reserve University, Cleveland, USA), covered how malaria has become endemic in 50% of the world. He explained how the absence of low-cost diagnostic tools and successful evaluation of infections in rural settings is the cause of incomplete malaria treatment. Zimmerman, in collaboration with Maciej Zborowski (The Cleveland Clinic

Foundation, Cleveland, USA), has used magnetic separation to detect malaria in the hopes of eradicating this disease. His studies in Papua New Guinea use the simple, but effective, technique of magnetic-deposition microscopy (MDM) to detect malaria-infected red blood cells by concentrating the weakly magnetic cells on a microscope slide using magnetic forces (Figure 1).

In the first session, which covered *Highlights in the Field*, Maxim Nikitin (Moscow Institute of Physics and Technology, Moscow, Russia) showed how his prototype device based on nonlinear magnetization could quantitatively and in real time measure magnetic particles in the tissues and bloodstream of mice. A linear response over a dynamic range of up to five orders of magnitude was reported. The next talk was given by Gary Zabow (National Institute of Standards and Technology, Boulder, CO, and National Institutes of Health, Bethesda, MD, USA). He talked about how magnetic particles make possible a completely new form of multispectral MRI. For this purpose, the magnetic particles are top-down microfabricated to produce distinct spectral contents that differentiate among particle types (Figure 2). This session was closed by the second invited speaker, Quentin Pankhurst (University College London & Davy-Faraday Research Laboratory, London, UK), whose talk focused on *Endomagnetism*, the science of sensing, heating and moving magnetic particles for diagnostic and therapeutic purposes. Pankhurst described how, by using a

superconducting quantum interference device-based sensor, he has, to date, detected the early stages of metastasized breast cancer successfully in the lymph nodes in 12 patients. The magnetic nanoparticles, which function like a magnetic dye, are injected into the tumor area 30 min before sensing. His group has also loaded hematopoietic stem cells with CD133-coated nanoparticles and has been researching their use in the treatment of atherosclerosis. Hyperthermia covered the last part of his talk. Improved particles for heat transduction, engineering new high-frequency circuits to make radiofrequency fields in controlled geometries and, finally, antibody-nanoparticle conjugation for tumor targeting are long-term goals in the treatment of metastatic cancer using hyperthermia.

In the second session, which covered the area of *Magnetic Drug Delivery and Gene Therapy*, Stefan Rovers (University of Technology, Eindhoven, The Netherlands) showed how a magnetic field can be used to switch on and off a polymeric drug-delivery system. Rovers pointed out that, by embedding iron oxide particles in a polymer film and applying an alternating magnetic field to produce heat, the diffusion coefficient of the drug dissolved in the polymeric carrier increases significantly. Release experiments showed an ON/OFF behavior, which was related to the iron oxide loading in the polymer film directly. Jin Chang (Tianjin University, National Institute of Nanobiotechnology, Tianjin, China) presented how a tat- and folic acid-mediated magnetic valproate-delivery system has promising utility in treating brain illnesses, such as epilepsy. Chang has investigated the distribution of ^{99m}Tc -labeled TAT-FA-VPA-LSMM by single photon emission computed tomography in rats. In his *in vivo* experiments, the therapeutic effects were

proven by electroencephalography (EEG), which showed a reduction in sharp waves and a normalization in the rhythm of the backdrop waves. Diandra Leslie-Pelecky (University of Nebraska, Lincoln, USA) reported that, by coating the magnetic particles with Pluronic® as a second layer over oleic acid, water-dispersibility was increased greatly. This surface modification also made the particles phagocytosis resistant and enhanced their circulation time. The particles are thus promising magnetic resonance (MR) contrast agents with increased T_2 -relaxation times. Neil Farrow (Keele University, Stoke-on-Trent, UK) closed the session by explaining how Magnefect™ has potential for *in vivo* gene therapy in the treatment of diseases, such as cystic fibrosis. The new aspect of this magnetofection technology is the utilization of oscillating magnetic fields. Results showed increased activity overall in *in vitro* transfection rates in many cell types (HEK, MG63, NCI-292 and human mesenchymal stem cells) in comparison to static fields and cationic lipids tested, no adverse effects on cell viability and rapid transfection times. Early animal studies show improved tumor transfection using nanoparticle-loaded macrophages as delivery vehicles. Further optimization through mathematical modeling, new magnet arrays, geometry of oscillations and new particle development should improve transfection efficiency even further.

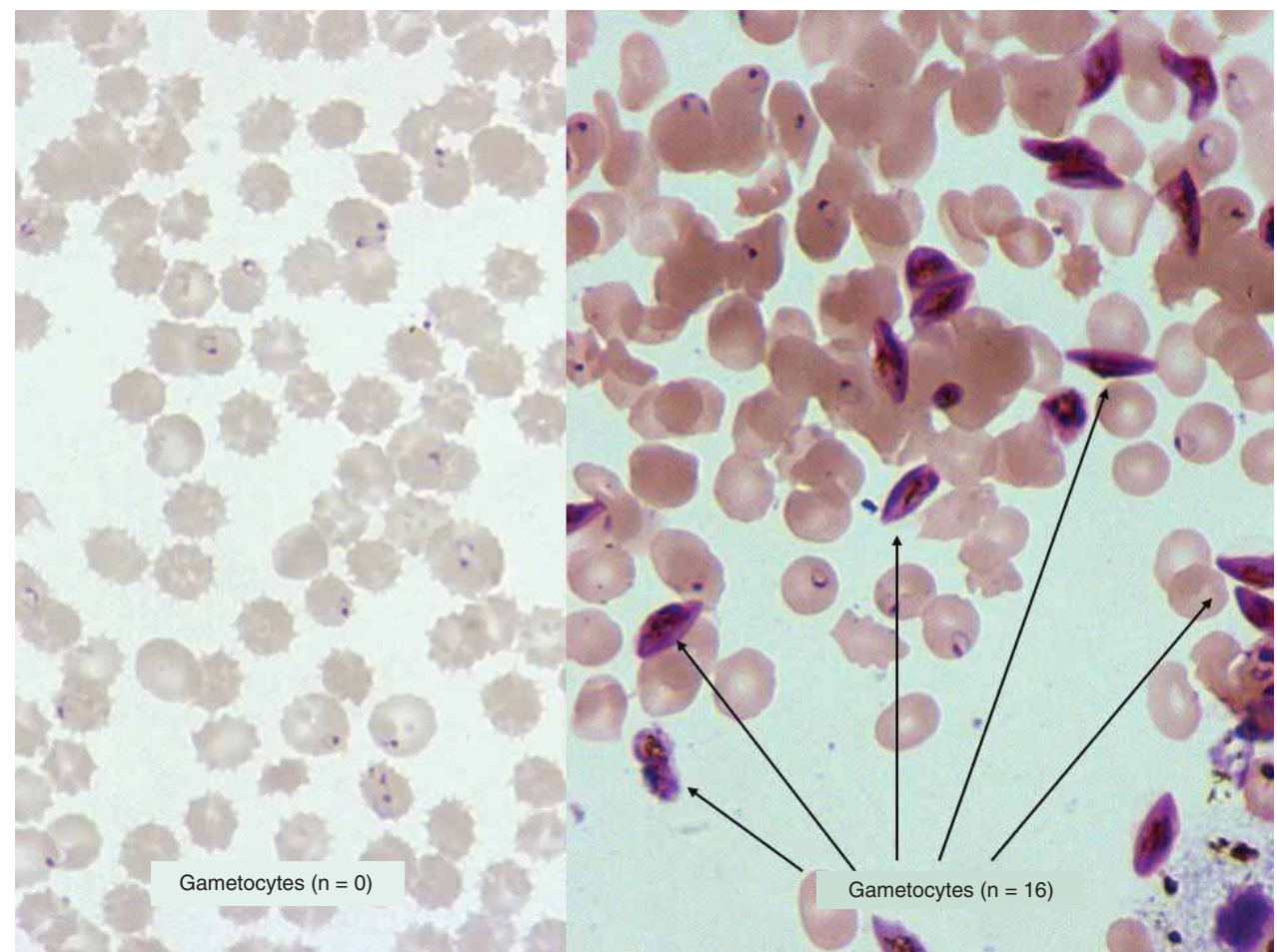
The third symposium was dedicated to *Nanoparticle Synthesis and Analysis*. Evagelos Athanassiou (Federal Institute of Technology, Zurich, Switzerland) presented a new generation of magnetic cobalt particles with carbon coating, which has advantages over the usual iron oxide-based particles. These particles are superparamagnetic with high mass magnetization and an inert coating. Using simple chemistry at room temperature, the particles' surface can be functionalized covalently. Mark DiIorio (MagneSensors Inc., San Diego, CA, USA) talked on the importance of ultrasensitive magnetic bioassays with applications, such as early detection of

bacteria, assessment of minimal residual disease in leukemia to better monitor and guide therapies and, last but not least, drug development and delivery. He believes that such assays will be the methods of the future, with high specificity and sensitivity. DiIorio clearly outlined the requirements for these magnetic particles: large magnetic moments, single crystal cores (30 nm), stable bioactive coatings, minimal aggregation, size between 50 and 250 nm and size variation dependent on the application. Under these conditions, rare cell assays to surface receptor mixtures of cells with less than 0.1% of the rare target cells are possible. A novel synthetic route to Fe–MgO nanoparticles using a solar vapor-phase condensation oven was presented by Carlos Martinez-Boubeta (ICMAB, Barcelona, Spain). He has also expanded this technique for universal application by taking advantage of laser ablation in solution. Environmentally friendly, controlled interparticle interactions, enhanced magnetic moment and non-toxic hydroxyl functionality on the surface are some of the advantages of the thus-prepared 2–200 nm particles. Work is ongoing to control size and shape of these particles. Stefan Odenbach (Technical University, Dresden, Germany), the third invited speaker, closed the morning session with an introduction to ferrofluids. He explained how magnetic fields induce a change of the rheological properties of ferrofluids and how this can cause changes in the thermophysical properties, especially the viscosity of the ferrofluid in a magnetic field. The magnetoviscous effects can be explained by formation and rupture of chain-like structures formed by large nanoparticles in a magnetic field. Using neutron scattering, microstructural changes have clearly been observed that are related to the changes in viscous properties of these particles. Odenbach finished by saying that the field-dependent changes of rheology may be crucial at any point where magnetic particle suspensions with sufficiently large nanoparticles are used in biomedical applications.

Robin Hicks (University of Victoria, Canada), the fourth invited speaker, talked about molecular magnets, which are materials consisting of molecular components that communicate through space and show magnetic properties. There have been intense efforts aimed at the development of alternatives to conventional magnets (metals and metal oxides or alloys); however, Hicks mentioned that the challenges on the way have been complex and formidable. Reacting *bis*(1,5-cyclooctadiene)nickel(II) ($\text{Ni}(\text{cod})_2$) with organic oxidizing agents with a 2:1 Ni:L stoichiometry (the opposite of the conventional ratio) results in a black solid compound with empirical formula $[\text{Ni}_2\text{A}(\text{O})_x(\text{H}_2\text{O})_y(\text{OH})_z]$, where x , y and z depend on L. Magnetic characterization of these compounds show spontaneous field-dependent magnetization and hysteresis at room temperature, with ordering temperatures well above ambient. These three compounds are members of a class of stable magnets that are at the interface between conventional inorganic magnets and genuine molecule-based magnets, said Hicks.

The next two talks then made clear that carboxylic groups are not the best and most stable functional groups for turning magnetite surfaces into biocompatible coatings. Sylvie Begin-Colin (Université de Strasbourg, France) investigated the binding of phosphate from phosphoric acid to magnetite with x-ray diffraction and Mossbauer spectroscopy, whereas Judy Riffle (Virginia Tech, Blacksburg, VA, USA) examined different block-co-polymers with phosphate functional end-groups using colloidal theories and stability measurements and compared them with carboxylates, amines and phosphonates. The conclusions of both investigators were similar. At pH 7 in water, all functional groups bind strongly to the magnetite surface but, once phosphate buffer – a main component of blood and other physiological liquids – is added, the carboxylates desorb quickly. Polymers adsorbed through terminal ammonium ions are displaced more slowly, whereas complexes containing phosphates remain stable on the magnetite.

Figure 1. Detection of malaria by conventional blood smear on the left compared with magnetic deposition microscopy on the right.



Preliminary studies showed that magnetic-deposition microscopy enriched the capture of malarial blood stages by more than 40-fold and, specifically, enriched the gametocytes necessary for human to mosquito transmission. During field studies in malaria-endemic Papua New Guinea, a sixfold higher prevalence of gametocyte-positive infected individuals was observed, suggesting a significantly higher potential for malaria transmission and increased challenge for malaria-control programs than considered previously.

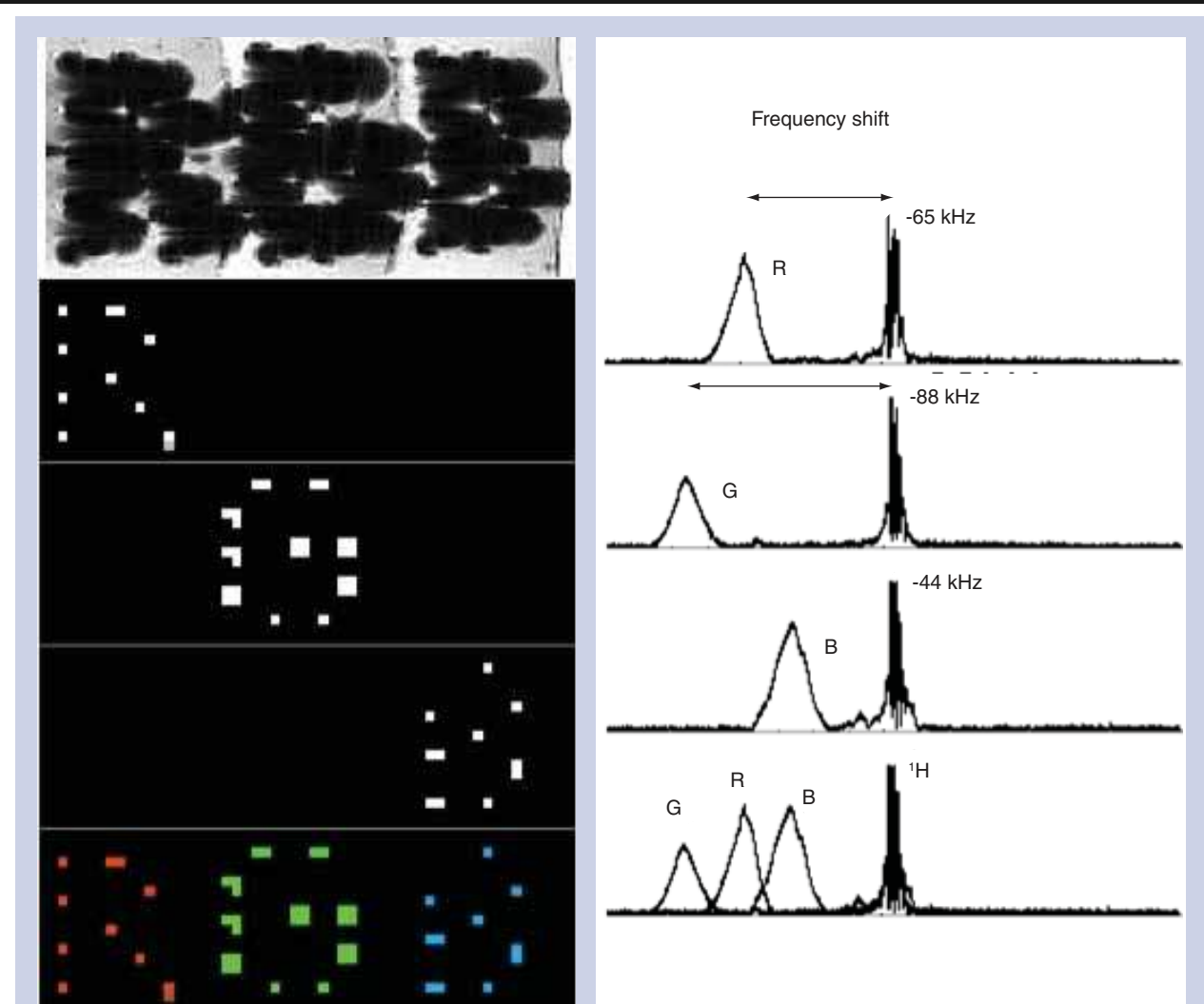
The fourth symposium was dedicated to *Hyperthermia*, specifically the heating effects that are produced when magnetic nanoparticles are placed in an alternating magnetic field. It was obvious from the talks by Cindi Dennis (National Institute of Standards and Technology, Gaithersburg, USA) and others that more information is necessary regarding the factors that influence the extent of heating or, in other words, maximize the specific-absorption rate (SAR) of magnetic nanoparticles. In very involved small and ultrasmall angle neutron scattering (SANS) experiments, Dennis found that three length scales are crucial for energy absorption.

They are the diameter of the magnetic core, the mean interparticle distance between the magnetic cores and the formation of collective structures possibly held together by magnetic interactions. Optimizing the magnetic-hyperthermia treatment for cancer therapy thus requires not only the choice of the best frequency and magnetic-field strength but also the use of monosized, equally and stably coated nanoparticles with defined behavior in a magnetic field.

The fifth invited speaker, Sylvain Martel (Ecole Polytechnique Montreal, Canada), closed the *Analytical Methods* session by showing us how a clinical

MRI system can be used to program the transport of magnetic particles in blood vessels. Martel pointed out that current magnetic-targeting techniques involve no navigation system on the particles and should thus be delivered (injected) as close to the target area as possible. Even in these circumstances, a significant quantity of particles is lost during magnetic targeting. These hurdles could be overcome by implementing three essential components – propulsion, tracking and control – for real-time controlled navigation of magnetic particles along pre-planned paths in the human vasculature. Using the three orthogonal coils of a conventional MRI

Figure 2. Micro-engineered magnetic particles provide local field control for high-sensitivity multispectral MRI.



Top-down micro-engineering enables unique spectral identification to be embedded in magnetic microparticles, enabling a new form of color tag for MRI. Below the regular gradient-echo MRI (top left), chemical-shift images and associated water spectra demonstrate this distinction between the different micro-engineered particle types.

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system and implementing additional software and control algorithms based on tracking information, Martel was able to send magnetic particles down a preprogrammed path. Among the many advantages of using an MRI machine are 3D imaging, enhanced tissue contrast, lack of radiation and, above all, the platform being already available in most hospitals, making technology transfers and acceptance easier, while reducing the cost of implementing the technology. Although it sounds a bit like ‘Star Wars’, this novel approach

might enable access to target areas deep in the human body with enhanced targeting efficiency under real-time navigational control.

The poster sessions this year were given extended time by holding them on two evenings. Under the guidance of Cordula Gruettner (Micromod, Rostock, Germany), a committee evaluated the posters and handed out prizes. Gernot Marten (Heinrich Heine University, Düsseldorf, Germany), Mei Lin Chan (University of California, Davis, CA, USA), Patricia

Stepp (University of Chicago, IL, USA) and Takeshi Hara (Tokyo Institute of Technology, Japan) won the first, second, third and the audience awards, respectively. Marten presented work on magnetic copolymer brushes in which particles were coated with a carboxyl-functionalized polymer that could be further bound to proteins. These particles collapse in the carrier medium on heating above the phase transition of the polymer of approximately 38°C, enabling separation of the particles in low magnetic

field gradients. Using this approach, he showed selective separation of trypsin from bovine pancreas solution.

In the *Imaging* symposium, Denis Markov (Philips Research Laboratories, Eindhoven, The Netherlands) discussed details of magnetic-particle imaging (MPI), a 3D imaging modality, which was presented as a world first during our last magnetic carrier meeting. The method capitalizes on the nonlinear response of magnetic materials to an oscillating magnetic field in a dedicated static-field arrangement. To make this technique successful, both the ongoing work on the hardware and a deeper understanding of the magnetic particle properties are necessary. Markov showed how particle size distribution, saturation magnetization and magnetic anisotropy are important for MPI and can be controlled by particle-synthesis parameters. In the imaging and biological-application symposium, it became clear that magnetic quantum dots have arrived in our field. Both Numpon Insin (Massachusetts Institute of Technology, Cambridge, MA, USA) and Christine Ménager (Université Pierre and Marie Curie, Paris, France) showed how these semiconductor crystals with spectrofluorometric advantages over traditional fluorescent dyes can be synthesized. Such hybrid particles can then be used as an MRI contrast agent or for optical and confocal microimaging.

The seventh session was dedicated to *Magnetic Separation*. Chris Earhart (Stanford University, Stanford, USA) spoke about a microfabricated sifter for high-throughput and high-gradient magnetic separation. Using nanotechnology, the sifter was manufactured by etching arrays of micron-sized slits on a silicon wafer and then depositing a soft magnetic film. In the presence of an external field, high-field gradients enabled the capture of the particles in the slits, followed by their release once the field has been turned off. Earhart achieved up to 60% separation efficiency for a single pass, which could be improved by placing multiple sifters in series. Nicole Pamme (University of Hull, UK) highlighted her group's

research on a microfluid device in which the magnetic particles act as maneuverable solid support for multi-step (bio)reactions in continuous flow. The particles are magnetically pulled across the different reagent streams that are generated along the flow chamber. During this process, multiple reactions and washings can be performed on the surface of the particles. Streptavidin-coated particles were labeled successfully with a fluorescently labeled biotin using this technique.

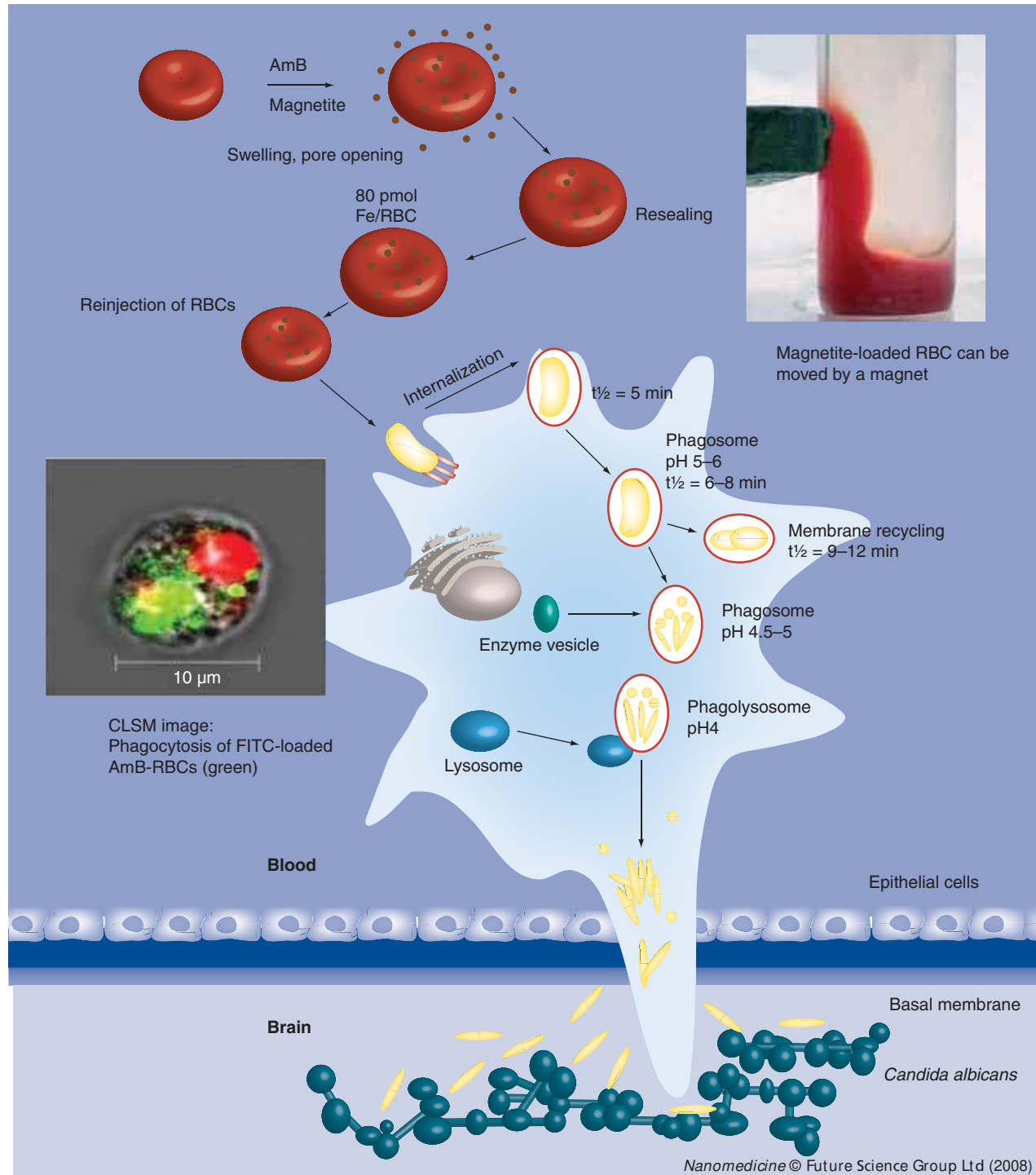
The eighth symposium was all about *Biological Applications*. Katayoun Saatchi (University of British Columbia, Vancouver, Canada) presented her ongoing work on using magnetic particles to regulate the diabetic heart metabolism. The early stages of cardiovascular disease (the leading cause of death in those with diabetes) are due to an alteration in the energy metabolism in a diabetic heart. As a result of impaired glucose utilization, the heart switches to increased fatty-acid uptake that causes mitochondrial dysfunction in the heart-muscle cells. Saatchi explained how she covalently bound heparin on magnetic particles and is using these heparin-modified particles to inhibit lipoprotein lipase. By reducing the activity of this enzyme, the fatty-acid uptake to the heart muscles can be reduced, leading to metabolic switching to glucose utilization and therefore a potential decrease in diabetic cardiomyopathy. Further research will magnetically deliver heparin microspheres to the heart capillaries to investigate, *in vivo*, the basic diabetic process of cardiomyopathy.

The final invited speaker of the meeting was Hans Bäumler (Charité - Universitätsmedizin, Berlin, Germany). He enlightened the audience on how red blood cells can be used as a taxi service for magnetically targeted drug delivery. He pointed out that particles are eliminated quickly from the body's circulation, that there is no or only uncontrolled passage of particles through barriers and that it is difficult to achieve therapeutic drug concentrations in the target tissues. By using red blood cells loaded with

magnetic, charged, hydrophilic/hydrophobic moieties, all of these difficulties can be overcome (Figure 3). Bäumler explained how they have loaded erythrocytes with amphotericin B (AmB) and luminescent magnetic particles and have also modified the erythrocyte surface with specific antibodies. With this approach, the red blood cells can deliver up to 10,000 times higher concentrations of AmB compared with liposomes, as stated by Bäumler. Furthermore, with only 750 AmB-loaded cells per ml of blood, the antifungal effects of AmB were reached. Bäumler mentioned that AmB can be replaced with any other water-insoluble drug. This, coupled with binding specific antibodies, would make an effective tool for targeting because the erythrocytes could transport the drug, reach the target and deliver/release the drug there.

The last symposium focussed on *Biosensors*. Joerg Schotter (ARC Seibersdorf Research, Vienna, Austria) showed how magnetic biochips are promising candidates for a diagnostic lab-on-a-chip. Magnetic markers were used for sample pre-treatment and target-molecule detection in which the particles, functionalized with primary antibodies against sepsis-indicative cytokines, were mixed with 10 µl of biological sample and injected into the microfluidic chip to be steered by gradient fields. The initial interaction between particles and sample is followed by a replacement step in which the sample solution is replaced with buffer leaving only the particles with surface-bound analyte behind. The particles are then steered further inside the flow channels to bind a secondary antibody enabling a sandwich immunoassay-type immobilization of the marker-bound cytokines. As explained by Schotter, the detection of the magnetic-stray field by the particles with the embedded magnetoresistive sensors is proportional to the aerial density of the particles. His ultimate goal is to have a system that is capable of detecting multiple targets in natural samples with no other input, thus creating a compact instrument good for point-of-care diagnosis. Mark Tondra (Diagnostic Biosensors, Minneapolis,

Figure 3. Red blood cells as magnetically targetable drug delivery devices.



Magnetite-loaded RBC can be moved by a magnet

RBCs were loaded with a nanosuspension of AmB and biocompatible, magnetic nanoparticles, which make them accessible for movement by external magnetic fields. In addition, the surfaces were modified with specific antibodies for targeting across the blood-brain barrier.

AmB: Amphotericin B; CLSM: Confocal laser scanning microscopy; FITC: Fluorescein isothiocyanate; RBC: Red blood cell.

USA) explained how commercially available strip tests (e.g., pregnancy tests) are detected with the naked eye. Although

inexpensive and useful for many applications, these tests fail to provide quantitative information – the result is just ‘Yes’ or

‘No’. Quantification can be achieved by using giant magnetoresistive sensors in a magnetically labeled immunoassay. Using

lateral flow strips that provide an easy-to-use biosample-delivery system, Tondra compared the strips to standard ELISA. This method has several advantages: no lab equipment is needed (plate reader, sample prep), set up is more compact and user friendly, the process is faster, no incubation and blocking steps are needed and the sensitivity is at least as high as ELISA. Optimization of the setup is ongoing.

The conference came to an end with the announcement of the next conference in Rostock, Germany, in May 2010. As everyone was leaving, one could hear and feel the success of the event among the discussions and goodbyes.

For more information regarding the meeting or magnetic micro- and nanoparticles in general, please check the frequently updated website [101].

Bibliography

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