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- Convergence of Nanoscience and Bioscience -

Abstracts

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Zur Eröffnung der Konferenz

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Leibniz-Institut für interdisziplinäre Studien e.V. (LIFIS)

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Es ist mir eine besondere Freude, Sie im Namen des Leibniz-Institutes für interdisziplinäre Studien und der Leibniz-Sozietät der Wissenschaften zu Berlin zu unserer 9th *Leibniz Conference of Advanced Science 2009* und des 1th *German-Russian Symposium on Nanobiotechnology – Konvergenzen von Nanoscience und Bioscience* – herzlich willkommen heißen zu dürfen. Wir wissen es zu schätzen, dass Sie sich daran beteiligen. Ein besonderer Gruß gilt den Referenten aus Deutschland und Russland sowie den institutionellen Partnern des LIFIS, die die Wissenschaft, die Politik und die Wirtschaft vertreten.

Die erfolgreich vorhergehenden Augustusburger Konferenzen nicht gerechnet, ist die heutige Leibniz Conference of Advanced Science in der neuen Reihe bereits die neunte. Alle orientierten sich konsequent an den – im Bild 1 der PowerPoint-Präsentation ausgewiesenen – praxisrelevanten Problemfeldern von hervorragender gesellschaftlicher Bedeutung sowie mit besonderen interdisziplinären wissenschaftlichen und wirtschaftlichen Herausforderungen, wobei die Kognitionstechnologie ein neues, weiter auszugestaltetes, exponiertes Element unserer Bemühungen repräsentiert. Das bewährte *Konzept der LIFIS-Konferenzen* – unsere „Konstruktionssystematik“ – vereint die bereit integrierten Problemkomplexe auf einer noch höheren Emergenzebene zu solchen Problemclustern, wie sie das Bild 2 hervorhebt. Ohne die *Interdisziplinarität*: das Prinzip (oder auch Paradigma) der wissenschaftlichen Strukturierung, Bearbeitung komplexer Probleme der Forschung und Entwicklung aus den unterschiedlichen Perspektiven, mit den jeweiligen Methoden und Theorien verschiedener Wissenschaftsdisziplinen (einschließlich der Sozial- und Geisteswissenschaften) und deren adäquaten Wiedergabe als ganzheitliche rationale Cluster, wäre das Verständnis für die Probleme und die Lösungsstrategien der Konferenzthemen weit weniger ausgeprägt.

Zahlreich sind die Belege dafür, dass sich – neben der *Informationstechnologie* – die *Nanotechnologie* mit all ihren komplexen und vor allem im hochdimensionalen Bereich der *life-science* zunehmend konvergierenden Forschungsfeldern – als eine maßgebliche und nachhaltige Grundlage für vielfältige wissenschaftliche, technisch-technologische, ökonomische, aber auch bereits spürbare soziale Umgestaltungen mit zweierlei Vorzeichen erweist.

Die Nano-, Bio-, Info-, Cogno-Convergence ist eine exponierte Version der anwendungsoffenen und rasch evolvierenden *converging sciences and technologies*. Mit dem Oberbegriff Technologie wird nach unserem Verständnis keineswegs auf die gegenständliche Produktion eingeeengt, wenn man unter Technologie generell das finale Zusammenwirken des Menschen mit technischen Artefakten oder operationelle Agentia aller Art zur gestaltenden Einflussnahme auf Stoffe, Energien und Informationen versteht.

Ob und inwieweit dabei die vernetzten Nano-, Bio- und Informationstechnologien mit den häufig zielsetzenden Kognitionswissenschaften „verschmelzen“ werden, wird zu beobachten sein. Weit wichtiger sind deren *Grundorientierungen*, die die US-amerikanische National Science Foundation (NSF) mit der These explizierte: „Converging Technologies for Improving Human Performance“ und die *weitere Qualifizierung der koordinierenden und integrierenden Prinzipien* der wissenschaftlichen

Strukturierung, Bearbeitung und Abbildung der komplexen Forschungs- und Entwicklungsprobleme in einem: der Inter- und Transdisziplinarität als Schlüssel zum Verständnis der Strukturen und des Verhaltens hierarchischer Systeme jeder Genesis von nano über mikro bis makro und zur Verwirklichung der generalisierenden Integrations- und Konvergenzintensionen der Wissenschaft.

Das verlangt von jedem involvierten Akteur und Betroffenen – und wer wäre das angesichts dieser Universalität nicht – eine besondere, wissensbasierte Aufmerksamkeit sowie ein verantwortungsvolles, antizipierendes Engagement.

Das LIFIS stellt sich als ein Mittler zwischen Wissenschaft, Praxis und Politik mit seiner bewährten Reihe Leibniz Conferences of Advanced Science bewusst diesem Anliegen. Die erwähnten Prozesse, ihre Ergebnisse (einschließlich der u.U. ambivalenten Wirkungen) sind selbst mit dem sinn- und anspruchsvollen, dialektischen Begriffsensemble <Komplexität, Inter- bzw. Transdisziplinarität und Konvergenz> heoretisch und praktisch nur unvollständig zu charakterisieren. Das bleibt uns bewusst, wenn wir mit unserer Konferenz entwicklungstypische Konvergenzen von Nanoscience und Bioscience in den Mittelpunkt rücken. Vor allem an Beispielen aus der biologischen Forschung und medizinischen Anwendungen sowie ihren natürlichen und technischen Pendanten sollen – ohne rhetorische Euphorie – die wissenschaftlichen, technologischen und ethischen Potentiale, der Einsatz der „ubiquitären Elektronik“ sowie der Mikro- und Nanosensorsysteme in der Diagnostik, der Telemedizin (insbesondere zum Telemonitoring) und als Assistenztechnologie für Menschen fortgeschrittenen Alters, aber auch die Risiken gentechnologischer (insbesondere nanobiotechnologischer) Entwicklungen sachlich dargestellt, kritisch beleuchtet und sine ira et studio bewertet werden.

Diesem interdisziplinären Anliegen haben wir – der Komplexität der Problemstrukturen und Lösungsalgorithmen entsprechend – Vertreter der Naturwissenschaften (insbesondere der Biowissenschaften, Physik, Mathematik, Materialwissenschaften), der Medizin, der Biomedizin und der Technikwissenschaften, wie der Elektronik, der Biotechnologie und anderer anwendungsorientierter Fachgebiete, aus Deutschland und Russland eingeladen. Wir freuen uns darauf, dass in unserem interdisziplinären Deutsch-Russischen Symposium zur Nanobiotechnologie renommierte Fachvertreter aus beiden Ländern in Form von „Vorträgen vor Vortragenden“ innovative Entwicklungen und Ergebnisse auf diesen Gebieten vorstellen wollen. Deren Anwendbarkeit auf die verschiedensten Fachgebiete und Lebensbereiche, ihre durchaus widersprüchlichen Auswirkung für die menschliche Gesellschaft werden wir diskutieren. Zudem *sollen* zukunftsweisende Entwicklungstendenzen auf dem Gebiet der Nanobiotechnologie in Deutschland und Russland beleuchtet und dadurch Wege für die bilaterale Zusammenarbeit vorgestellt sowie die Realisierung unterstützt werden. Wesentliches Ziel ist es, das nanotechnologische Potential von Biomolekülen und die Nutzung diesbezüglicher Erkenntnisse in den vielfältigen Anwendungen für die menschliche Gesellschaft zu skizzieren, nationale und internationale Kooperationen zu generieren und die Öffentlichkeit umfassender zu informieren.

Fachliche SCHWERPUNKTE unsere Konferenz bilden demgemäß:

- Nanoeffekte, Nanomaterialien und Nanosensoren,
- Nanokomponenten und -systeme in Biologie und Technik,
- Prozesse der Selbstorganisation in makromolekularen und kolloidalen Systemen,
- Bioverträglichkeit/Nanotoxizität und Zuverlässigkeit von Nanokomponenten,
- Bioinformatische Herausforderung und Potential der Genomforschung,
- das Genomprojekt und Personal Genomics,
- Nanoapplikationen in der Biomedizin und der klinischen Diagnostik.

Ich wünsche unserer Konferenz einen guten Verlauf, Ihnen produktive Diskussionen, reiche und nachwirkende Anregungen sowie einen angenehmen Aufenthalt in Lichtenwalde. Den Sponsoren unserer Konferenz gebührt ein besonderer Dank. Allen voran dankt das LIFIS dem Bundesministerium für Bildung und Forschung, welches das involvierte 1. Deutsch-Russische Symposium Nanobiotechnologie als Projekt entscheidend fördert und damit überhaupt erst ermöglicht.



DNA – A whole nanoworld in one molecule

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Information and biotechnology are the both future technologies of 21st century. Whether nanotechnology will subordinate or occupy its equivalent position beside these both technologies should be demonstrated by the most fundamental natural product, the desoxyribonucleic acid (DNA). There is no other biomolecule which influenced significantly the picture of modern biology and biomedicine in the last years.

DNA is a highly symmetric molecule which encodes the information of life by a 4-bit-code of 4 nucleobases adenin, cytosin, guanin and thymin. In general it consists of a double helix and presents a clear scalable nanostructure. DNA save the whole genetic information in a high compact matter. It could be counted a sthe world largest and best hard disk. Storage density is 2 bits per cubic nanometer, which is comparable to 10^{12} Gbit/ 1cm^3 . Comparable densities on computer hard disks is about 10-100 Gbit/ 1cm^3 . Natural existing DNA synthesis machines are much more effective and faster in data processing as currently existing computers.

The architecture of DNA double helix allows the exact nanoscaling of this biomolecule from 0.4 nm to many millimeters. Generation of well defined DNA molecules is possible by DNA processing enzymes or artificial substrates. The most prominent technology of in vitro amplification of DNA is the polymerase chain reaction (PCR). PCR was the basic method for performance of the world`s most important research approach, the Human Genome project, whiche decodes the the primary sequence of the human DNA.

The application of DNA processing in the widest sense allows also the generation of nanostructrues in the classical field of nanotechnology like nanofabrication, synthesis of novel materials, nanolayers, biosensors or membran components. DNA structure and synthesis allows incorporation of artificial components and the native properties as an isolator could be overcame to design nanowires and allows nanoelectricity.

Nanomachines based on the combination of DNA molecules and other biological molecules like proteins or enzymes are able to performed enourmous work by a nanocosmic space requirement. Most of known properties of nanocomponents or nanosystems are existing intrinsicly in a DNA molecule or could be induced by modification or integration of it in complex applications.



Gene targeting with modified oligonucleotides

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Oligonucleotides encoding for interesting DNA sequences, i.e. abnormal cancer information, are biotechnical tools both to analyze and to control gene expression. Here we focus our report on the gene targeting approach based on the triplex strategy. Though this approach has a great potential for diagnostics and therapeutics up to now this approach has not been applied yet, because of the limitations concerning the triplex-forming oligonucleotides (TFOs) especially under native conditions. The TFOs need to overcome these barriers in order to become effective diagnostics and therapeutics as well as to apply them routinely.



FEL RADIATION USE FOR LARGE BIOMOLECULES ABLATION

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The main goal of this work is: an investigation of a possibility of using terahertz radiation for transfer biomacromolecules and nanoparticles from a solid surface into the aerosol phase. We have show that this process is nondestructive – the ablated molecules conserve primary structure. We applied this technique to standardization of the biochip production and express analysis of nanoparticle's size. We named the process of biomacromolecule and nanoparticle transfer into the aerosol phase the soft nondestructive ablation.

To check the nondestructive character of the soft nondestructive ablation method of biomacromolecules under action of trahertz emission we used three different bioanalytical techniques. First, to monitor a possible loss or retention of the enzymatic activity of a horseradish peroxidase sample we employed histochemical staining. After ablation, horseradish peroxidase particles were collected from the aerosol phase onto the solid filter. By the method developed by BioRad company we checked that the horseradish peroxidase sample retained its enzymatic activity after ablation. Second, by comparison of the electrophoretic mobility of the original and the ablated horseradish peroxidase samples we proved that this complex protein was undamaged. Major part of the enzymatic activity is associated with the high molecular weight fractions. This fraction was very similar to the control sample. Third, we present the experiments proving the nondestructive character of ablation by the MALDI-TOF technique. It was shown a very good correlation of the molecular mass-spectrum of native and ablated horseradish peroxidase samples.

Ablation of the mixture of DNA plasmid pUC18 (2.8 tpb) and lambda phage DNA (48 tpb) was carry out. To prove the nondestructive character of the soft nondestructive ablation method of DNA macromolecules we transformed E. coli competent cells by the ablated plasmid. We compared of the electrophoretic mobility of plasmids extracted from E. coli transformed by native and ablated plasmid samples. The electrophoretic mobility of both samples was the same.

The principle of soft nondestructive ablation of biological macromolecules under terahertz irradiation was applied to the direct analysis of the target DNA from biochip surface. The synthetic DNA-probe of 17 nucleotides was covalently bonded to the surface of a silicone plate. A target DNA from 90 nucleotides was hybridized to the DNA-probe like on the usual biochips. The target DNA on the biochip model is fixed by the hydrogen bonds. By action of terahertz emission we can destroy the hydrogen bonds, left the covalent bonds intact and transfer the target DNA into the aerosol phase. Start of ablation was controlled by the aerosol spectrometer and then the target DNA was collected to the filter for the subsequent analysis by sequencing. After ablation the target DNA was collected by the filter washed out and amplified by PCR. The target and ablated DNA sequences were identical. So we have got the method for the direct analysis of the target DNA.

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Development of cellular assays for automated microscopy to measure multiple parameters by single cell High Content Analysis

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Repetitive experimental protocols such as toxicology tests, siRNA assays or drug screening that require sample analysis by microscopy are highly time consuming. High-content imaging is an microscopy technology that begins with automated image acquisition and concludes with data analysis. This process integrates image analysis and subsequent transfer of the numerical data into statistical representations such as graphs, heat maps and tables. The main focus of this technology lays on transferring automatically acquired images into meaningful data that can easily be interpreted and published. The power of high-content imaging resides in the ability to measure not only fluorescence intensity and morphological changes, but also temporal and spatial dynamics. This technology allows also to perform multiplexed assays that simultaneously measure and analyze a large number of such cellular parameters. However, multiplexing is often restricted due to reagent, assay, and instrumentation limitations. BD Biosciences is addressing this by developing specific instrumentation, assays, reagents, and software that enable such multiplexing. We will highlight the capabilities of the BD Pathway™, such as kinetic and confocal imaging, and the impact these features have on high-content imaging. In particular, we will address several challenging applications including stem cells and neurobiology. In addition, we will discuss the development of a line of BD™ Bioimaging Certified reagents that have direct impact on the ability to multiplex. To facilitate the use of antibodies for imaging applications, BD Biosciences embarked on a screening process to evaluate a large library of monoclonal antibodies for utility in bioimaging applications. The library of antibodies included specificities that recognized proteins involved in cell signaling, cell cycle, apoptosis, cancer and neurobiology. Antibodies were tested using 3 cell lines and several fix/perm methods that are relevant to high-content imaging applications on automated platforms. Specific criteria regarding signal to noise, sub-cellular localization and other important parameters were used to qualify reagents. Two distinct Bioimaging Certified reagent product lines resulted from this antibody screen. One is a continually expanding collection of currently greater than 200 unlabeled primary antibodies that have been shown to have general utility in bioimaging applications. The other is a subset of these reagents that have been further developed into primary conjugated antibodies to facilitate multiplexed high content analysis with monoclonal antibodies. These reagents, combined with an automated imaging platform, will enable the rapid development of novel cell-based assays. To enable live-cell assays we developed an environmentally controlled on-stage chamber with an integrated pipetting system in combination with an automated fluorescent microscope for imaging of individual cell cultures in multi-well plates. The broad range of assay types include nuclear protein translocations, live/dead cell detection, intracellular calcium dynamics and various measures of the apoptotic cascade like Caspase-3, JC-1 distribution and nuclear fragmentation. For another parameter, DNA strand break count we demonstrated the effect of utilizing our confocal imaging technology to improve the quality of the data by achieving higher z'-scores. The use of our Neurite Outgrowth and Angiogenesis algorithms will demonstrate the capacity to detect differentiation and morphological changes depending upon exposure to various stimuli. Furthermore new applications such as intracellular bacterial count, cell cycle analysis and the multiplexing of intracellular calcium concentration measurements with mitochondrial membrane potential assessment will be discussed. Our data will show that live-cell imaging of kinetics and endpoint parameters together with high-resolution confocal microscopy is a powerful tool for exploring cellular events in multidimensional space and time.



Computation of Material Properties at the Nano- and Atomic Scale

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The unbroken trend of scaling electronic circuits has led deeply into the subnanometer region which is especially true for gate electrodes that today only consist of a few atomic layers. This is nanoelectronics even if it is still called microelectronics. In many other fields, artificial structures and devices reach nanometer and atomic scales. For such small material regions the discrete atomic structure of the materials has to be considered by means of quantum mechanics. Until recently this was only possible in a very limited fashion due to the heavy computational burden of quantum mechanical computations.

On the other hand, in the last decades we have a dramatic development of computational technologies and resources. This development makes it reasonable to apply quantum mechanical computations to solid state nanoscale structures and many other applications. The most basic level of such computations are “*ab initio*” methods. These methods use only the data of the periodic system of elements and do not need any further parameter. They are computationally very intensive and difficult, but on the other hand they are equivalent to experiments. Thus for the fast developing of computational technologies and resources, these methods will be increasingly used to save time and money in research and industry.

This presentation will discuss *ab initio* and atomic scale computational principles and their wide range of applications.



Low Temperature Superconductor Electronics

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Over the past decades there has been an impressive improvement in the performance of semiconductor devices. In particular, the speed and the number of gates on a chip (integration scale) have improved exponentially year on year. However, over the recent years the clock frequency does increase only slowly. With a few GHz it hits a fundamental limit that hardly can be improved further for devices based on electrical charge transfer. This holds also for semiconductor devices scaled down to nanometre size. The problem is not the intrinsic speed of the single transistors, but rather the power that is needed to switch at higher frequencies. The increasing energy that is dissipated during each fast logic operation leads to high power requirements of the chips and makes it increasingly difficult to remove the heat from the chip again.

Since the discovery of the Josephson Effect in 1962, the application of superconductivity to electronics has been a challenging field of research and development. Whenever both high clock frequencies and low power dissipation are major requirements, superconductor digital electronics has unique potential that allows to overcome the speed limit of the conventional semiconductor electronics. The intrinsic switching time of superconductor electronic devices is very short, on the order of a few picoseconds. Even more important is the low power dissipation on the order of microwatt per gate, a thousand times less than CMOS circuits.

The modern concept for the superconductor electronics is based on a family of digital devices that exploit a unique property of superconductors, the magnetic flux quantum. Such digital circuits are called nowadays SFQ (Single Flux Quantum) devices. Single magnetic flux quanta can be easily generated in a few picoseconds time and processed by means of Josephson junctions. The SFQ pulses serve as the carriers of the binary information depending on whether or not they appear during on clock cycle at the output of the device.

When SFQ technology became popular in the late 1980's public funding, in particular in Japan and in the U.S., has enabled rapid progress in this field and as a result several RSFQ IC foundries were established worldwide and are operating to this day. In Japan there are fabrication facilities at NEC and SRL, in the U.S. at HYPRES, NIST, and TRW, and in Europe at IPHT and PTB, both in Germany, at VTT in Finland.

The talk reports briefly the basic principles of SFQ technology, the current status of chip fabrication, and overviews some of the application fields. Some selected future developments are discussed as well.



Gel forming supramolecular polymer complex used as drug delivery matrix

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Different natural gels fulfil manifold functions in the physiology, e.g. different mucosa varieties support transport processes, synovial fluid provides the lubricant property of joints, and the vitreous body in the eyes achieves mechanical stabilization of bulb and retina. The medical technology has developed gel forming substitute materials in order to compensate malfunctions caused the loss of physiologically necessary gels.

One of typical age-related disease is the degeneration of the vitreous body associated with the decrease of the gel volume. The change of volume causes mostly the detachment of the retina. Patients of diabetes mellitus are also living under enlarged risk of proliferative retinopathy (PDVR). Ophthalmic surgery for repair and fixing the retina requires a total vitrectomy (extraction of the vitreous). The reattachment of the retina is usually stabilized by tamponades like silicon oils or fluorinated liquid hydrocarbons. The unavoidable emulsification of tamponades requires their replacement after every 3 to 12 months. Furthermore, the risks for cataracts on the lenses and neoplasm at the iris increase significantly. Until now, biocompatible materials as artificial vitreous body are not available.

A novel hydrogel system on the base of adamantane and cyclodextrin containing oligomers or polymers has been developed as artificial vitreous body. The supramolecular host-guest polymer complex is enabled to form transparent and retina stabilizing hydrogels. Free cyclodextrin functions can be used as carrier supporting a continuous drug release for ophthalmic therapies like reducing the intraocular pressure (glaucoma).

Cyclodextrin complexes will be used as drug delivery system in medical substitutes of toenail avoiding onychomycosis and nail bed infections, as well as supporting the nail regeneration. Nano-encapsulated drugs or food ingredients achieved by supramolecular interactions with cyclodextrin, as well as embedded in micelles or liposomes, provide a broad range of formulation, the adjustment of the drug release performance and bioavailability.



Synthesis and Characterization of Silicon Nanowires: Towards Devices and Applications

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Semiconducting nanowires have the potential to impact many technologies either through improved material properties or by size effects. With silicon still being the most important semiconducting material in microelectronics and for photovoltaic devices, much of the silicon nanowire (SiNW) research is focused on electrical properties.

The SiNWs can be grown by the vapor-liquid-solid (VLS) method using chemical vapor deposition (CVD) from silane. The VLS process is based on the formation of nanosized liquid droplets of a catalyst metal, such as gold, forming a low temperature eutectic with silicon, and the dissolution of Si, provided e.g. by cracking a gaseous precursor into the alloy droplet until at supersaturation nucleation and growth of NWs occurs at the solid-liquid interface. The NWs can be doped during growth by adding PH₃ or B₂H₆ to the process gases, and successful activation of the dopants in the wires was demonstrated using electron-beam induced current imaging. Structurally the NWs are single-crystalline, and they can show different growth directions depending on the growth conditions.

Alternatively, SiNW arrays can be made from Si wafers by a wet chemical etching method. The wires show an increased surface roughness compared to that of VLS-grown wires. Interestingly, wires etched from highly doped wafers show a strong photoluminescence, which can not be related to oxygen containing species at the surface of the wires.

In view of possible applications VLS-grown SiNWs were used as a substrate for matrix-free laser desorption ionization (LDI) mass spectrometric analysis of lipidic species with lithium salts as dopants. SiNWs require much lower laser energy to desorb molecules due to the strong optical absorption coupled with heating of the silicon core within the insulating oxide sheath and the relatively low thermal conductivity of the SiNWs.

Gold capped SiNWs can also act as efficient surface-enhanced Raman scattering (SERS) substrates. The Raman signal can be enhanced even further when silver is deposited onto the caps by autometallography. Mapping of the SERS intensity reveals a strong SERS signal over the entire sample area. Nanowire-based photovoltaic structures are currently of great interest due to their potential to reduce manufacturing costs while allowing to keep good efficiencies and device lifetimes.

Several SiNW based thin film solar cell concepts like those with radial p-n junctions or solar cells fabricated by wet chemical etching of multicrystalline silicon layers on glass or are currently under investigation. For sensor applications SiNW based field effect transistors are developed. The SiNWs are functionalized with different molecules to achieve a high sensitivity towards the analyte in the presence of confounding environmental variability. The goal is an inexpensive sensor to detect various volatile organic compounds.



DNA-detection using nanoscale metal structures

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In the last years metal nanoparticles showed the potential to play an important role in a range of applications, for example in microscopic visualization, molecular construction and various bioanalytical techniques as alternative markers for the detection of biomolecules. Based on their various unique properties different approaches for the detection of nanoparticle labeled biomolecules, for example electrochemical, optical and gravimetric methods were developed. Here, we introduce a way for the nanoparticle based electrical detection of biomolecules. The used nanoparticles were synthesized by the enzyme horseradish peroxidase [1]. Due to the enzymatic reaction we were able to improve the sensitivity as well as the specificity of a developed chip based electrical biomolecule analysis technology [2]. It is based on the electrical detection of biomolecules immobilized in a gap between two microstructured electrodes. By the enzyme induced growth of nanoparticles, silver is deposited on the bound biomolecules and lead to bridging the electrode gap and consequently to an increase in the measured conductivity over the gap. In this presentation we introduce the process of the enzymatic synthesis of silver nanoparticles and the application of these nanoparticles in biochip technology.

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Microreaction Techniques: Challenges between Continuous Nanoparticle Synthesis and Fluid-based Nanoengineering

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Micro reaction technology uses fast heat and mass transfer and opens new process windows for continuous-flow chemical processes. Beside the progress in molecular synthesis, it represents an important step to generate new classes of nanomaterials, for generating and managing hierarchically structured materials and liquid phases. The handling of large numbers of small volumes enables micro reaction technology for combinatorial synthesis and highly parallelized screenings.

The potential of microfluidics for nanomaterial synthesis is demonstrated by the micro continuous-flow synthesis of different kinds of nanoparticles. It is shown that the homogeneity of nanoparticles is improved and different nanoparticle types can be addressed. The micro segmented-flow technique is particularly suited for separating smallest reaction compartments and for addressing complex concentration spaces for screenings. Microfluidics improves not only the experimental methods and products. It develops to an interface between matter, material properties and process data. So, it allows the integrated handling of substances, particles and particle-related data and becomes, therefore, a tool for managing nanoobjects, for constructing nanosystems and for storage and processing of nanoobject-related informations.



Nanopores for transport of proteins through biological membranes: molecular translocation machines of mitochondria

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Mitochondria are essential energy transducing organelles in virtually all eukaryotic cells. They have a complex architecture. They are built by two different membranes: the outer membrane (OM) and the inner membrane (IM), the latter one containing numerous deep invaginations into the matrix space, the cristae.

The biogenesis of mitochondria requires the activity of two genetic systems. The vast majority of the some 800-2,000 different proteins that make up mitochondria are encoded by the nuclear DNA and only some 8-13, depending on the species, are encoded by mitochondrial DNA. The nuclear encoded proteins are translated in the cytosol as precursor proteins and imported into the mitochondria. These proteins contain sequences which function as signals for import into the mitochondria. They need a highly complex and diverse set of molecular machines to be translocated into the organelle and to be modified and assembled to supramolecular complexes. So far six translocation complexes have been described, comprising some 50 proteins that mediate translocation.

The lecture will concentrate on two of these complexes, the TOM complex in the OM and the TIM23 complex in IM. The TOM complex represents the entry gate for almost all mitochondrial proteins. It is composed of seven different proteins which on the one hand serve as receptors recognizing precursors to be imported and, on the other hand form a nanopore that allows the passage of unfolded or nearly unfolded precursor polypeptide chains. The TIM23 complex mediates transfer across both OM and IM into the matrix and insertion of proteins into the IM. The two complexes form a supercomplex during protein translocation.

The TIM23 complex can be operationally divided into two parts, the membrane part or translocon, and the import motor. The membrane part is made up by at least five different subunits which comprise a second receptor and a voltage dependent protein conducting channel. The membrane potential is required to mediate the transfer of matrix targeting sequences (usually located at the N terminus) across the membrane.

The import motor is associated with the membrane part on the matrix (trans) side of the IM. It represents a highly complex molecular machine, consisting of five different proteins. The motor mediates threading of the unfolded precursor polypeptide chains. It can unfold folded domains of precursor proteins that are present at the outside of the mitochondria. The energy for translocation and unfolding is provided through the hydrolysis of ATP in the matrix. The key player in this molecular motor is the mitochondrial heat shock protein Hsp70, a molecular chaperone that can bind incoming unfolded polypeptide chains and release them in an ATP dependent manner. Other subunits of the motor part serve as “accelerator” and “brake”. A large body of evidence suggests that the motor works in the manner of a Brownian ratchet.



Inorganic nanoparticles in self-organized biopolymer complexes and self-assembled composite nanobiofilms

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Integration and assembling of nanocomponents of different nature into novel hybrid systems opens possibilities for design and creation of new functional nanomaterials with advanced or even novel properties important for practical applications. We report on the preparation and characterization of new self-organized hybrid bio-inorganic nanostructures and nanocomposite nanofilm materials based on the complexes of natural (DNA, polyamines, hyaluronic acid) and synthetic polyelectrolytes with inorganic nanoparticles (CdSe, magnetic iron oxides, noble metals). Experimental strategies used for preparation of nanomaterials were based on a number of synthetic and physical-chemical methods (interfacial and bulk phase synthesis and assembly, ligand exchange and substitution, polycomplex formation, chemical binding and competitive interactions, layer-by-layer assembly, self-assembly and self-organization, DNA templating and scaffolding). Electron microscopy, SPM, spectroscopy techniques were used to characterize the prepared nanostructures. It was observed that interactions of colloid inorganic nanoparticles with complexes of native linear DNA molecules can result in formation of organized quasi-linear nanoparticulate structures. New nanostructured biohybrids based on the complexes of natural polyamines, DNA, hyaluronic acid and noble metal nanoparticles (Au, Pd, Ag) were synthesized. New approach to fabrication of highly-organized nanocomposite nanofilm materials representing the free-floating films composed of chemically bonded nanoparticles have been developed based on the controlled processes of self-assembly and self-organization of colloid nanoparticles via the formation of their complexes with polyfunctional ligands in a bulk liquid phase in the absence of any surfaces and interfaces. New biohybrid nanofilm free-floating sheet-like nanocomposite magnetic material based on the complexes of spermine and magnetite nanoparticles was synthesized in a bulk aqueous phase. It was found that the energetic balance between electrostatic repulsive interactions and attraction due to the chemical binding of nanoparticles via bridge ligand molecules had substantial effect on the morphology of the formed nanofilm material and allowed efficient control of its structural characteristics. The possibilities for use of the prepared magnetic free-floating nanofilm material in the magnetic separation technologies and other applications will be illustrated and discussed.

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Dynamics of Brownian cycle swimmer

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We discuss the motion of self-propelled colloidal particles, which move along circles rather than along a straight line when their driving force does not coincide with their propagation direction. Examples include confined bacteria and spermatozoa, catalytically driven nanorods, active, anisotropic colloidal particles and vibrated granulates.

Using a non-Hamiltonian rate theory and computer simulations, we study the motion of a Brownian "circle swimmer" in a confining channel. A sliding mode close to the wall leads to a huge acceleration as compared to the bulk motion, which can further be enhanced by an optimal effective torque-to-force ratio. Our findings are supported by recent experiments on motile microparticles derived from *listeria monocytogenes*.



Biocompatibility of micro- or nano-sized biomaterials?

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The clinical problem: Implants for Joint replacements generate wear particles of different size distributions. Examples are demonstrated for various pairings of materials. The cellular and tissue reactions are driven by the interaction of different cell types. Macrophages play an important role in this reaction.

Therefore cytokines of macrophages after phagocytosis of nano- or micro-sized corundum, graphite and chromium oxide were investigated and compared to negative and positive, i.e. lipopolysaccharide stimulated, controls. Light-, scanning- and transmission electron microscopy of the macrophages, their behaviour in culture and the production of cytokines on the gene and protein expression levels were investigated.

In these experiments with a macrophage cell line (RAW264.7) stimulated by model particles of corundum, graphite and Cr₂O₃ with nm and µm size and identical mass, different genes were up- or downregulated.

Secreted cytokines and chemokines were effective to stimulate or inhibit cell growth, cell division or apoptosis and cell fusion. Nanometer size particles proved more active in secretion of proinflammatory cytokines than µm size particles.

An option to pharmacologically treat failing implants could be the inhibition of proinflammatory cytokines or chemokines.



Influence of microstructures and coating with amorphous diamond-like carbon on the growth of adherent cell lines

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Especially in the field of implantation biology and cell cultivation routines the properties of material surfaces are of great importance for the adhesion of cells. Most times a rapid and effective settlement with cells is desirable. Hence, the influence of laser-generated surface structures in combination with a carbon coating on plastic surfaces for the settlement of adherent cells was examined.

The structuring was carried out with an excimer laser. Polystyrene surfaces were structured with grids of 8 to 100 μm width and different geometry. In addition, some of the structured surfaces were coated by laser pulse deposition with a tetrahedral hydrogen-free amorphous carbon layer (ta-C) with a thickness of 50 to 100 nm. Furthermore polystyrene surfaces were coated with ta-C without additional structuring. On these three surface types the adherent cell lines were tested for their growth behaviour. The dependence of cell adhesion, morphology, vitality and proliferation on the chosen structure and coating variations were investigated by fluorescence and laserscanning microscopy as well as vitality assays. The colorimetric MTT assay has proven to be particularly suitable for analysis. It is based on the intracellular metabolism of a substrate to the photometrically measurable formazan.

The experiments confirmed the biocompatibility of the ta-C layer. The ta-C coating on unstructured surfaces did not change the growth behaviour. Mouse fibroblasts (cell line L929) showed 25% increase of growth density and an improved adhesion of the cells with right-angled structures (8 μm bar width, 50 μm gap width). On additionally ta-C coated structures a 75% higher growth density was noticed. The rat endothelial cells (NRK52E) showed a doubling of cell density with the same surface treatment. The contact inhibited mouse fibroblasts (cell line NIH3T3) responded to the surface structuring with a growth density decrease of appr. 20%.

Numerous experiments show that surface structures with dimensions similar to cell size and additional surface coating with ta-C stimulate growth of some of the adherent cell lines.

Future investigations will pay special attention to nanostructures generated with laser pulse coating in the ta-C layer because these structures may play a special role in cell adhesion. In addition, the effect of doping the ta-C layer will be analysed with regard to inhibition or increase of cell growth.



Interaction of Cells with Biologically Functionalized, Multicompartment Polyorganosiloxane Nanoparticles

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The research related to the synthesis of increasingly complex nanoparticles heads towards desired properties such as specific targeting, enclosure of different drugs, and/or multiple marking, leading to multifunctional and multicompartment nanoparticles. Polyorganosiloxane nanoparticles offer a wide range of possible modifications finally leading to multifunctional and multicompartment nanoparticles[1]. The synthesis of the nanoparticles is based on the well known hydrolysis and condensation of alkoxy silanes. Subsequent modifications allow the introduction of different functionalities, leading to the desired properties. A schematic picture of a particle is given in Figure 1.

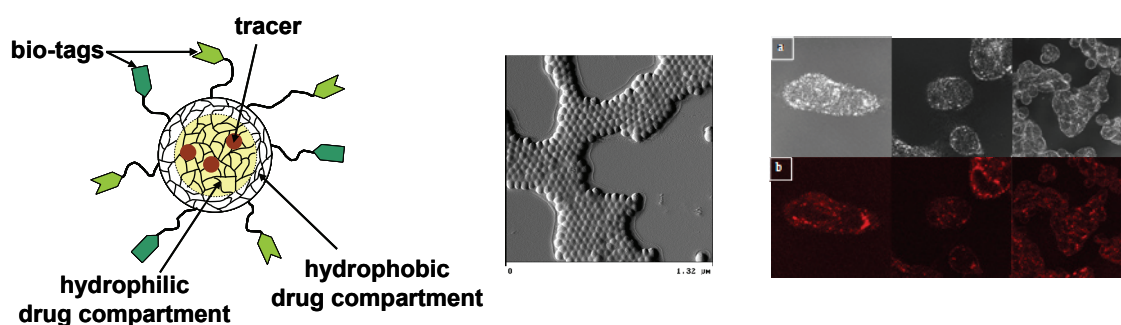


Figure 1

Left: Schematic picture of the nanoparticles; middle: AFM micrograph of the nanoparticles; right: uptake of the nanoparticles into MDCK II cells (top: light microscopy, bottom: fluorescence image).

We will present an example of fluorescently labelled, oligo-DNA modified nanoparticles, describing the synthesis, characterization and results obtained from cell uptake studies (e.g. in Figure 1), demonstrating the versatility of the approach.

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One- and two-dimensional microtoxicological screenings in nanoliter-fluid segment sequences with fast micro photometric and bead-based fluorimetric read-out

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The investigation of biological effects of an increasing number of compounds, in particular the need for toxicological evaluation, demands new miniaturized analytical strategies. Microreaction technology is very suitable for a variety of such screening processes. Unlike conventional bacterial culture and detection methods, which rely on incubation of a sample to increase the concentration of bacteria to detectable levels, miniaturization leads to a completely new approach for biological screening and investigations, with consistent reduction of uncontrolled parameters in a single experiment due to a high number of different combinations of parameters which can be substituted at once. Segmented flow technique - droplets of aqueous solution embedded in a fluorinated carrierfluid - provides a simple platform for manipulating samples with no dispersion or losses to inter-faces. In this manner, a much better analysis of synergistic or compensatory effects of environmental parameters on biological systems can be gained. This way, a better understanding about the variability of individual responses to chemical, physical and biological effectors within apparently homogenous populations can be achieved. For the analysis, however, conventional methods can not be applied due to the small volumina of samples. Therefore a non-invasive measurement system for determination of pH inside microfluid segments has been developed. Polymer microparticles containing an immobilized pH-sensitive dye are used for determination of pH inside microfluid segments. As part of the experiments carried out, the concentration-dependent response of an *Escherichia coli* culture for the effector 2,4 - dinitrophenol (DNP) and combinatorial effects for the effectors 2,4 - dichlorphenol (DCP) and gold nano particles was determined. Large sequences with up to 400 microfluid segments containing gradually varying concentrations of the effectors were generated using a PTFE microfluid arrangement, including a 7-port manifold and PC-controlled syringe pumps. The response of the cell culture was characterized by a double sensor system allowing a simultaneous read out of metabolism-related changes as well as changes in cell density. A twin arrangement of a micro flow-through photometer and a micro flow-through fluorometer in connection with the application of pH-sensitive polymer sensor particles was installed. This experimental setup allowed a detailed determination of drug-related changes in fluorescence intensity and cell density by the *E. coli* culture. In summary, the application of the segmented flow technique for multi-parameter drug screenings provides new insights into the biological answer of bacteria cultures cultivated at nanoliter scale.



FROM BASIC GENETICS TO BIOMEDICAL APPLICATIONS

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Institute of Cytology and Genetics is unique in the diversity of the problems covered by its research, which has no analogs in the Russian genetics. The Institute is able

- To perform basic research in practically all fields of the modern genetics;
- To study genetic systems and processes at any level of hierarchical organization of the living systems; and
- To conduct interdisciplinary research at the interface of genetics and other fields of knowledge (physics, chemistry, and Earth sciences).

Many projects that were commenced from solving purely basic problems in genetics form the background for innovation developments at the Institute.

Virtual screening and computer design of chemical compounds targeted to identified sites in protein structures are performed using an integrated approach involving the methods of computer systems biology and protein structure analysis, including modeling of molecular genetic networks of the biological processes associated with development of pathologies; identification of the key genes and proteins in the reconstructed molecular genetic networks; detection of the regulatory circuits, cycles, and critical links significant for functioning of the molecular systems; search for the sites in the spatial structures of the target proteins responsible for protein–protein interactions, for the active centers, the sites of allosteric regulation and posttranslational modifications, and so on.

The Institute is involved in the basic research aimed at development of the approaches to design of the new-generation drugs based on immobilization of biologically active components on inert carriers using electron beam technologies.

The Institute has a solid background in the field of molecular diagnostics. In particular, we focus on the development of DNA diagnostics of bacterial and parasitic disorders, non-communicable diseases and genetic disorders.

The basic research of the Institute provided for creating the technology for manufacture of biologically active food supplements and drugs using the higher fungus *Ganoderma lucidum*, intended for therapy and prevention of cancer and other diseases. The biologically active supplements and drugs of this fungus are very popular and demanded in the world medical practice due to their safety in combination with a high pharmacological activity. These preparations are most powerful immunity stimulators and are known as cancer prevention and therapy tools and drugs for cardiovascular diseases (hypertension and atherosclerosis).

A unique collection of experimental genetic animal models reproducing widely spread human diseases has been created at the Institute. The developed models are an efficient tool for clarifying the molecular genetic and physiological mechanisms underlying the development of pathological states and designing the pharmacological means for their prevention, correction, and treatment.

The majority of these innovation opportunities are connected with the results of basic research, and this a combination of basic and applies sciences actually underlies our advantages.



Interrelation between nano- and micro levels in genome organization

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The comparative analysis of polymorphism of DNA fragments, flanking by the inverted repeats of decanucleotides (RAPD), microsatellites (ISSR) and terminal sites of retrotransposones (IRAP) in genomes of different breeds of domestic species (cattle and sheep) and populations of closely related wild species (*Bison bonasus*, *Bison bison*, *Ovis nivicola borealis*) was carried out. DNA regions with the high conservatives on the length were observed. Possible connection of such conservatives with the belonging of DNA flank fragments to purin/pirimidin tracts was discussed. It was coordinated well with the hypothesis of Lima de Faria about the "chromosomal fields" about close relations between nucleotide sequences and chromosome morphology.

With the use of DNA arrays the comparative analysis of profiles of the gene expression of two pigs organs, liver and kidney was carried out. 40 genes were revealed, which expressions were essentially above in kidney, than in liver. The possible sources of mistakes in analysis of gene expression profiles caused by "cross" hybridization of one probe with different cDNA of gene transcripts of the genes belonging to gene super families, the same cDNA with different probes were discussed. The basic differences between profiles of the gene expression in kidney in comparison of liver had appeared connected with the genes supervising ionic exchange, and also mechanisms of cellular division. It was corresponded well with dominating participation of kidneys in maintenance of ionic balance in blood and also with lowered activity of cytokinesis in a liver (polyploidy of hepatocytes).

It was demonstrated the possibilities to use of the short DNA fragments for in-depth studies of "chromosome phenotype", genetic-biochemical mechanisms of cellular and tissue phenotype formation.

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Microfluidic Biochips in the Analysis of DNA

Peter Riege Key Account Manager
febit biomed, Heidelberg

The talk gives detailed information about febits proprietary suite of microfluidic microarrays and instruments. It will show the principles of the probe synthesis directly inside the microchannels as well as advantages of arrays architecture for the reproducibility and automatisisation of the complete microarray experiment.

Examples for the main applications supported by our company – mRNA expression profiling, miRNA expression profiling and enrichment of DNA for targeted re-sequencing with next-generation massive parallel sequencing platforms will be given.



Fluorescence labeling technology: from tube to animal.

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Fluorescent labeling technology are being used increasingly in immune and DNA assays and diagnostics, molecular biosensors, microscopy and small animal whole body imaging (fluorescence tomography) as well as drug detection and drug discovery in *in vitro* and *in vivo* approaches. Numerous and growing numbers of color fluorescent proteins like GFP and RFP, lanthanide chelates, room temperature phosphorescent labels, polymer nano particles and quantum dots are providing dramatic improvements in sensitivity of assays, efficient background signal rejection, real-time measurements, high throughput screening *in vitro* and *in vivo*.



Nanoengineering of therapeutic and diagnostic antibodies

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Recombinant therapeutic antibodies can be classified as pharmaceuticals with unique characteristics. Being produced *in vitro*, these antibodies are either completely identical to natural human proteins that are formed by immune system or very similar to them in terms of their structure and function. Antibody-based therapeutics belong to the mostly fast-growing segment of the world pharmaceutical market. The development and production of therapeutic antibodies consists of several steps: discovery of target and its validation, obtaining of antibodies and nanoengineering of their structure for the improvement of the therapeutic potential (chimerization, humanization), production of recombinant antibodies in appropriate hosts, pre-clinical and clinical studies.

At the Biological Faculty, the technology for the construction of therapeutic antibodies was developed, and several antibody candidates for the treatment of various diseases were produced and studied at the laboratory level and soon will be evaluated in the pre-clinical tests. A representative set of monoclonal antibodies against aflatoxins, hazardous carcinogens present in food and feed, was obtained. The panel of antibodies was characterized at functional and genetic level, nanoengineering tools were applied to improve their diagnostic properties by means of structural modification of the antigen-binding regions.



Bead-based multiplex assays for autoimmunity screening

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The detection of autoantibodies (AAb) is essential for the diagnostics of autoimmune diseases. The differentiation of AAb is done by specific tests like bead-based multiplex assays. Multiplex assays allow the detection of multiple AAb in parallel at the same time.

This technology is based on combination of microbeads with automated microscopy. Microbeads are coded by two fluorophores.

The ratio of these fluorophores is detected for decoding of each microbead population. Fluorescence intensity of the third fluorophore on the surface of the microbeads, measured in every bead population, reflected the average AAb reactivity of the serum sample.

Microbead-based immunoassays may improve serological diagnostics of autoimmune diseases and may serve as a way to standardize aAb analyses.



Nanobeads-based express-diagnostics of bacterial infections

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Nanosized beads have colloidal properties in liquids. Coupling of specific antibodies to the surface allows the aggregation of large complexes of many nanobeads in the presence of specific antigen. These complexes are visible with naked eyes and do not require specific equipment. This technology is very suitable for express-diagnostics because the generation of these nanocomplexes is very fast and could be performed in any laboratory. Nanobead-based immunoassays may improve serological diagnostics of infectious diseases.

Express-diagnosis of common, family endotoxin and its species of gram-negative bacteria in blood serum of patients with septic diseases and infectious complications after cardiovascular surgery, general surgery and extracorporeal profile in blood serum of donors in 10 minutes (17 test systems) as MAP-Endotoxin spp. (to detect endotoxin (LPS) to all gram-negative bacteria), MAP-Pseudo. spp. (to detect general endotoxin (LPS) *Pseudomonas*), MAP-Pseudo. aeru (to detect endotoxin (LPS) *Pseudomonas aeruginosa*), MAP-Pseudo. cepa (to detect endotoxin (LPS) *Pseudomonas cepacia*), MAP-Pseudo. fluor. (to detect endotoxin (LPS) *Pseudomonas fluorescens*), MAP-Pseudo. malto. (to detect endotoxin (LPS) *Pseudomonas maltophilia*), MAP-Pseudo. stutz. (to detect endotoxin (LPS) *Pseudomonas stutzeri*), MAP-Enterobac. spp. (to detect general endotoxin (LPS) *Enterobacter*), MAP-Enterobac. cloa. (to detect endotoxin (LPS) *Enterobacter cloacae*), MAP-Enterobac. aero (to detect endotoxin (LPS) *Enterobacter aerogenes*), MAP-Enterobac. alpha (to detect endotoxin (LPS) *Enterobacter alpha*), MAP-Kleb. spp. (to detect general endotoxin (LPS) *Klebsiella*), MAP-Kleb. pneu (to detect endotoxin (LPS) *Klebsiella pneumoniae*), MAP-Kleb. oxy (to detect endotoxin (LPS) *Klebsiella oxytoca*), MAP-Serra. spp. (to detect general endotoxin (LPS) *Serratia*), MAP-Serra. marc, (to detect endotoxin (LPS) *Serratia marcescens*), MAP-Serra. & Enterobac. (to detect endotoxin (LPS) *Serratia* & *Enterobacter*) were worked out and implemented into clinical practice in Bakoulev Scientific Center for Cardiovascular Surgery RAMS in Moscow, Russia.

This express-diagnostic test-system allows controlling rationality therapies used an antibiotic and leads to economy of using the antibiotics for the patient and to reduction the patient being in a hospital. They also can be used when acts of terrorism, natural disasters, car accidents and etc. taking place.



Magnetic nanoparticles in medicine: future diagnostic and therapeutic applications

Gunnar Glöckl, Werner Weitschies

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Magnetic nanoparticles (MNP) are widely used in technical but still rarely in biomedical applications. However, there is various research endeavor to extend to future applications.

We are investigating MNP for different diagnostic applications *in vitro* as well as *in vivo*. The methods are based on the differing relaxation behavior of freely movable and immobilized particles. Furthermore, we are investigating MNP for therapeutic applications like magnetic hyperthermia or magnetic drug targeting.

For all research topics, the particle characteristics, particularly the anisotropy energy, is a crucial parameter. We therefore put much effort in the characterization of particle size distribution and the direct measurement of the anisotropy energy as well.