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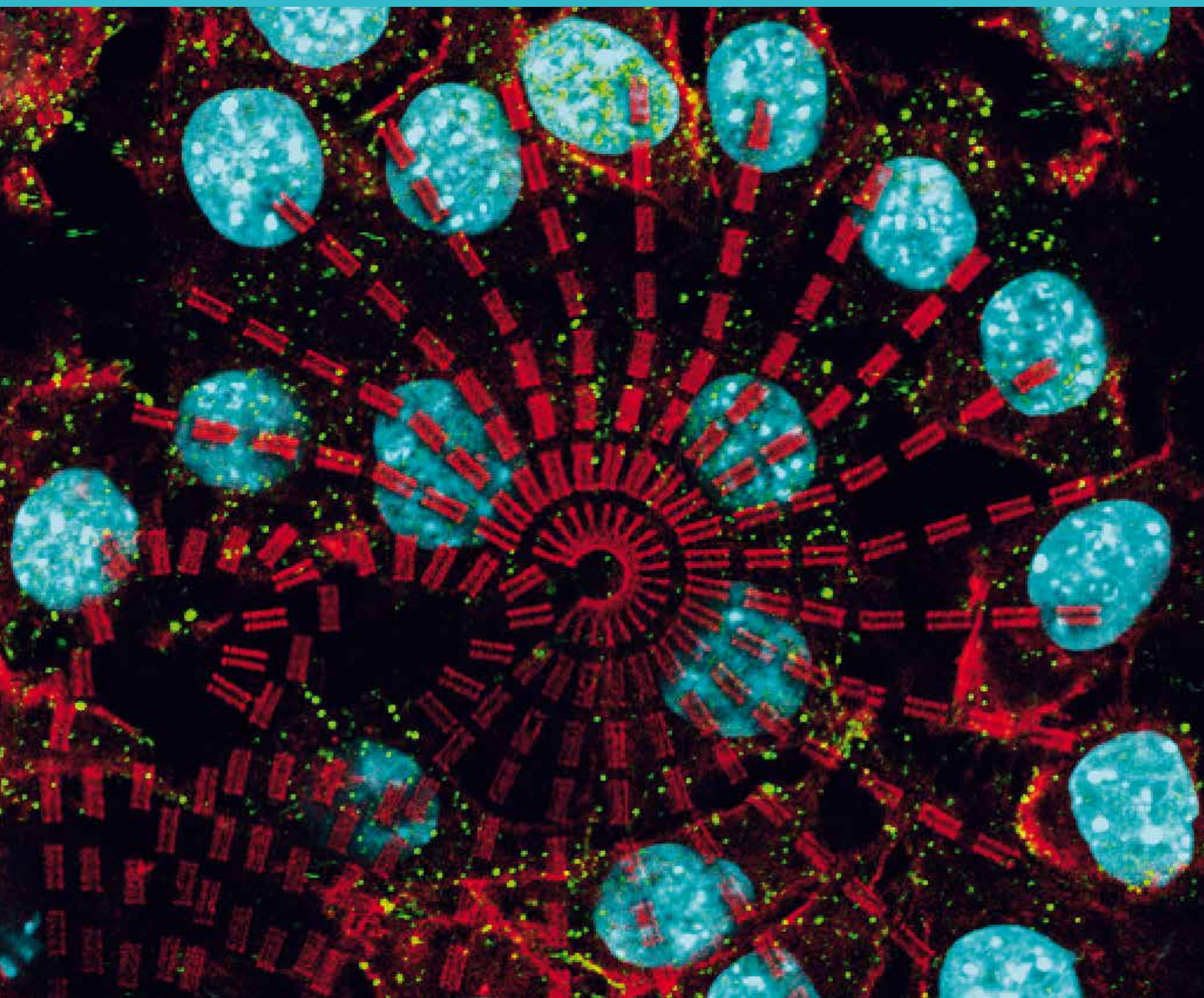
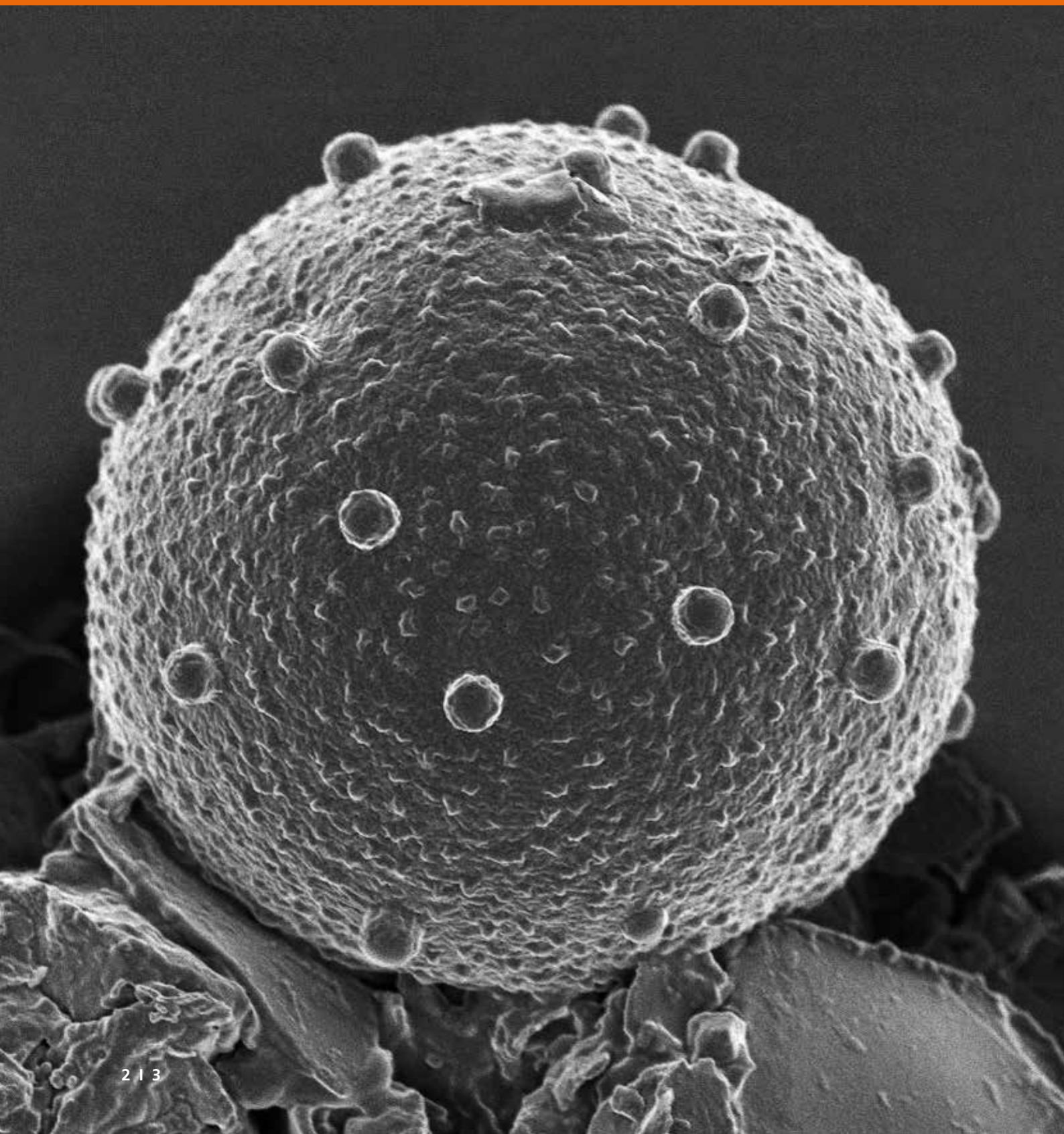
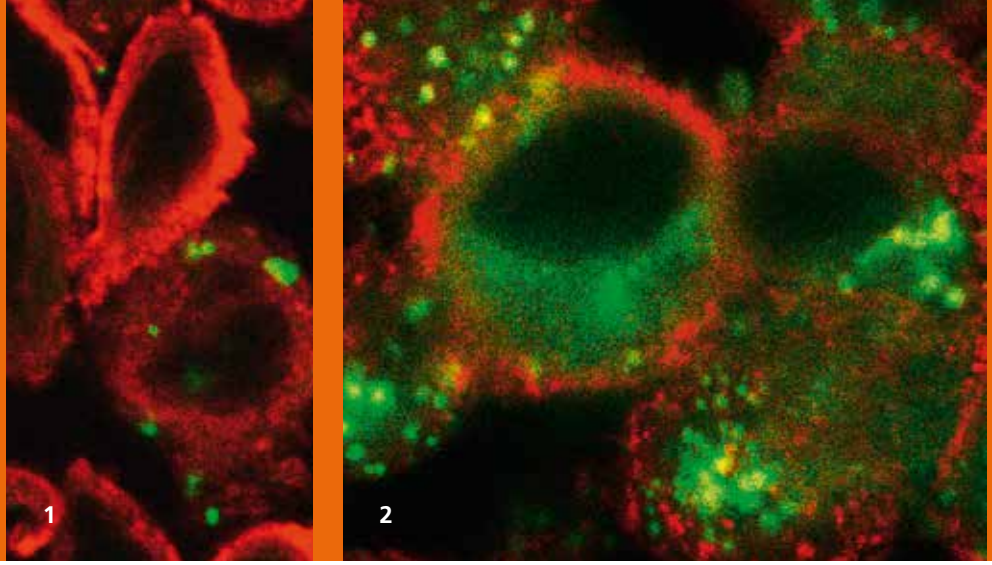
FRAUNHOFER GROUP FOR LIFE SCIENCES

NANOTECHNOLOGY RESEARCH FOR MAN AND THE ENVIRONMENT



POTENTIAL AND OPPORTUNITIES





Uptake of nanoparticles by cancer cells:

1 *Unmodified*

2 *Ligand-modified*

International estimates suggest that nanotechnology will contribute to the value added of products with a market value of 3 trillion US dollars worldwide by the year 2020. The technological and economic significance of nanotechnology is tremendous, and its status as one of the key technologies of the 21st century is justified – above all in Germany. Germany is one of the leading countries in nanotechnology. Nearly half of all European nanotechnology businesses are based in Germany, and between 50,000 and 100,000 jobs in this country at present directly or indirectly depend on nanotechnology.

Dwarfs creating giant opportunities

The term nanotechnology derives from the old Greek word "nános", roughly meaning "dwarf". It thus alludes to the size of particles, interfaces, and functional structures which account for the special characteristics of nanotechnological applications and products. There is, as yet, no generally accepted definition of this term.

In many research areas, however, the following description has become widely established: nanotechnology is the production, investigation, and use of structures, molecular materials, and interfaces with at least one critical dimension being smaller than 100 nanometers. This means that a nanofiber or nanotube can, in fact, have a length of several millimeters – as long as its diameter is less than 100 nanometers it will still comply with this definition.

Seizing opportunities and preventing possible hazards

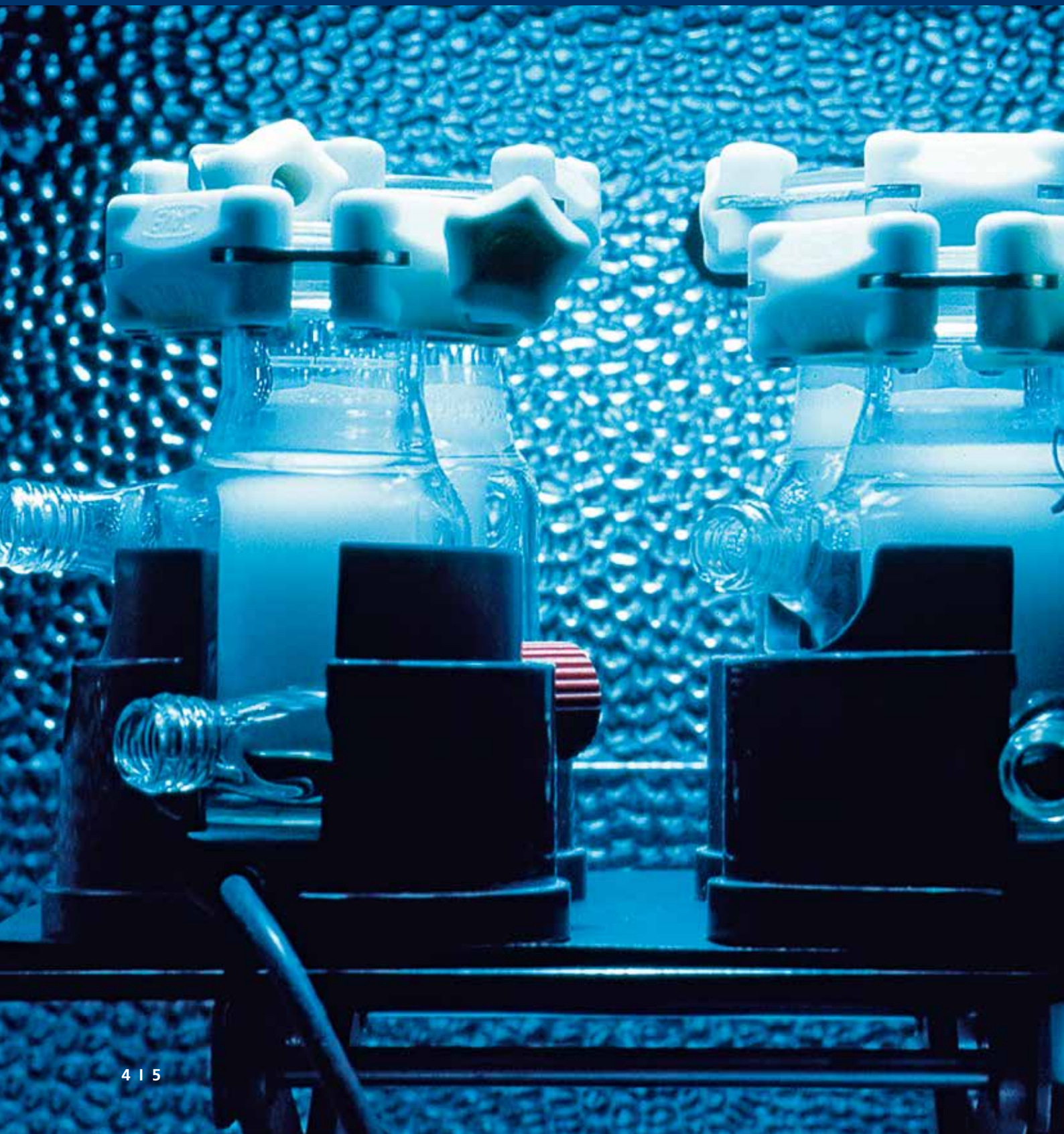
The wide spectrum of possible applications in medicine, environmental protection, packaging technology, production engineering, and the economic potential make nanotechnology a truly compelling field of research and motivate mankind to exploit the benefits. Past experience, however, has shown that technological innovation may also involve risks. According to the precautionary principle, therefore, special research effort in the area of hazard assessment and safety evaluation is imperative. Many questions still remain unanswered.

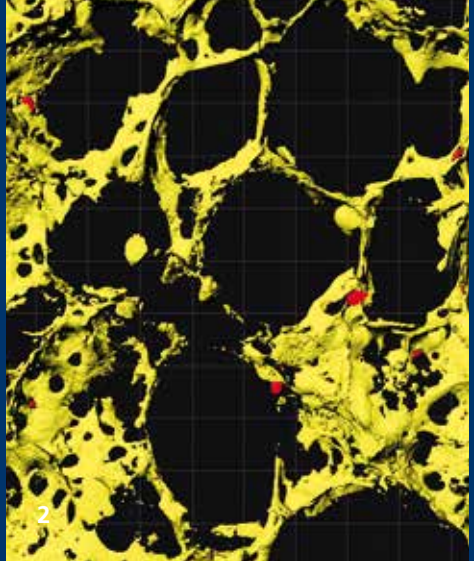
The special properties and high reactivity of nanomaterials are due to their small size. Indeed, this is the reason why existing methods for hazard and exposure assessment need to be modified in order to account for nano-specific aspects.

The institutes of the Fraunhofer Group for Life Sciences are researching a wide range of aspects of nanotechnology, for example new applications in medicine and novel methods for pollutant degradation to protect the environment. Another focus within the Fraunhofer Group for Life Sciences is sustainability, which aims foremost to ensure an appropriate balance between the preservation and use of resources. This is why Fraunhofer researchers are also intensively studying the potential hazards of nanotechnology and are pioneers in a novel scientific discipline – nanotoxicology. They are developing methods to show to what extent and under which conditions nanomaterials may have toxicological significance. They are conducting studies to find out whether nanomaterials have an impact on natural habitats such as water and soil, how they behave in biological systems such as cells, organs, and organisms, and to what extent nanoparticles in packaging materials may be released and migrate into the packaged goods. Potential emissions of nanoparticles during the processing of nanoparticle-containing composites are also being investigated.

Anybody wanting to efficiently and sustainably use next-generation technologies such as nanotechnology is required to actively look into the potential consequences and carry out risk assessment of these technologies. The Fraunhofer Group for Life Sciences is committed to meeting this need.

POTENTIAL





1 *Biochip based on functionalized nanoparticles.*

2 *Precision-cut lung slices with live/dead staining.*

RESEARCH FOR MEDICINE

According to expert opinion, Germany is the worldwide leader in the nanotechnology area which is currently experiencing the most rapid growth, namely the development of nanotechnological applications for the healthcare sector. Nanotechnological methods are expected to lead to novel diagnostics and therapeutics. These could enable faster diagnoses, earlier assessment of therapeutic success, and more efficient use of therapeutics. The partners cooperating in the Fraunhofer Group for Life Sciences are researching this innovative approach, creating new opportunities for patients and healthcare providers.

Biodegradable and biocompatible nanoparticles

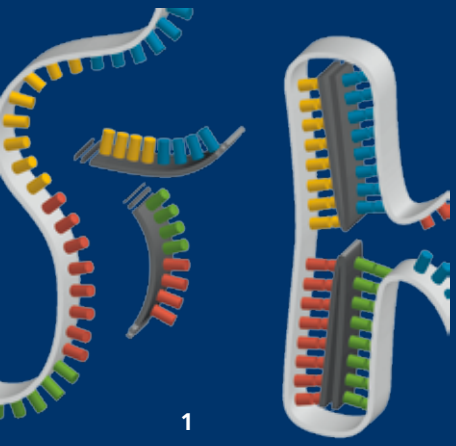
Polymeric nanoparticles can be used as carriers for the controlled release of active pharmaceutical ingredients. Increasingly important in this context are biodegradable compounds which, once they have fulfilled their purpose in the organism or the environment, are broken down into harmless degradation products. The physical and chemical properties of biodegradable polymers depend on their functional groups. The combination of nanoparticles with therapeutically relevant proteins allows new pharmaceutical concepts to be experimentally explored.

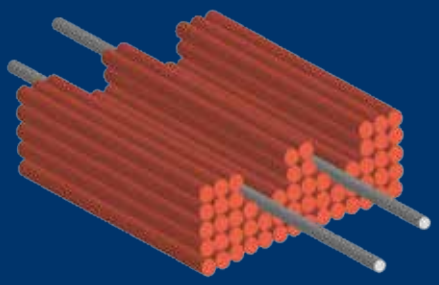
Nanoparticle-based carrier systems are versatile: they protect sensitive pharmaceutical substances from premature degradation in the organism, but may also release the active agents in a targeted manner. Fraunhofer researchers have developed biocompatible block copolymers. Using the emulsion method, they use these polymers to produce biodegradable nanoparticles into which therapeutic protein compounds such as cytokines or growth factors can be encapsulated. Once released from this capsule, the active substances again display their original bioactivity.

In order to ensure that the polymeric nanoparticles, with their load of active substance, actually head for the intended target cells (drug targeting), they can also be functionalized with specific surface properties such as, for example, proteins. Once the nanoparticles have reached their target in the organism, they do not release the active substances randomly, but rather according to a predefined kinetics. The release kinetics are controlled via the molecular weight and the ratio of hydrophilic to hydrophobic monomer units. We are thus in a position to adapt our polymeric matrix systems as well as the biodegradable and biocompatible block copolymers under a variety of aspects to meet our clients' different requirements.

Protein biochips based on functional nanoparticles

Proteins belong to the basic molecules of life. Their functions, structures, and interactions are the base building blocks for biomedical research, diagnostics, and new therapies. Due to a lack of appropriate methods, protein research up until now has concentrated on proteins that are stable and easy to handle. Fraunhofer scientists are now expanding the range of methods. Using functional nanoparticles they are developing microarrays, i.e. special biochips, which due to their modular





1 *DNA origami.*

2 *Carbon nanotubes, adjusted to DNA.*

structure can be adapted to meet a large variety of needs. Depending on the client's specific requirements, the Fraunhofer Group for Life Sciences can functionalize the microarrays with a wide variety of functional groups, to which biomolecules in turn can be bonded.

This highly versatile research tool allows trace concentrations of proteins to be detected, measured, enriched, and analyzed using state-of-the-art spatially resolved MALDI mass spectrometry.

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DNA nanosystems for biomedical applications

Arrangements and patterns of nanometer-sized molecules are key factors in many biological processes. Cutting-edge therapeutic approaches involving analysis of specific cell types or the triggering of cellular reactions are becoming more and more dependent on the ability to control the space, orientation, and number of molecules in the nanometer range.

Currently, the most advanced method available to construct nanometer-sized multifunctional structures is a method referred to as programmed self-assembly of DNA and other nucleotide-based biopolymers. Taking into account a few simple rules, it is possible to construct complex objects with exactly predefined shapes and molecular compositions. These objects can be made significantly smaller than was possible with any previously available method. They can be used as matrices for the exact placement of almost any type of molecule. Furthermore, they can perform functions which are triggered by external signals. Their complete biosafety is particularly important for medical applications.

With this technology the research of the Fraunhofer Group is exploiting two large application areas. On the one hand, nanoparticles can be used for targeted application of therapeutically active agents and signals (drug delivery). On the other hand, they can be employed to design molecular matrices in the development of diagnostic tools or reactive nanomaterials. For example, carbon nanotubes can be arranged with nanometer precision, so that new biosensors can be developed.

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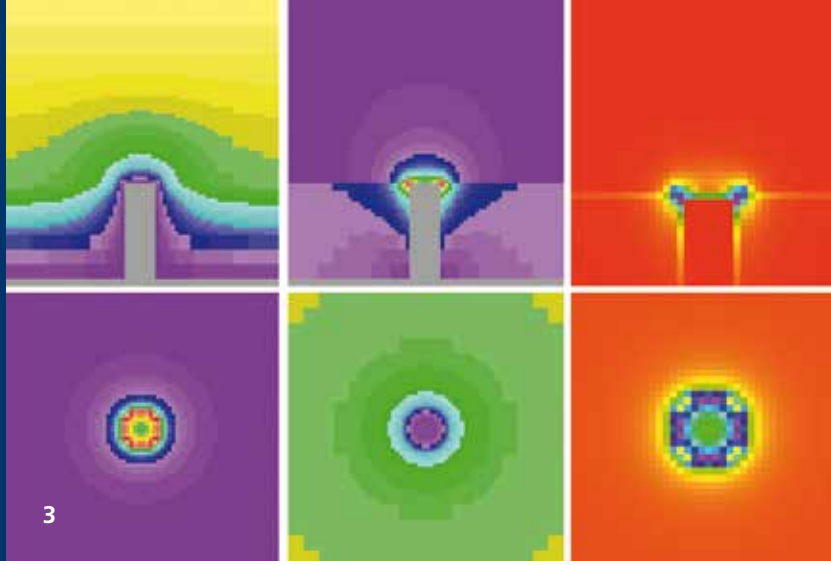

3 *Field simulation around a nanoelectrode: electric potential, field strength, and field strength gradient (from left to right).*

Magnetic nanoparticles in medical diagnostics

At present, complex and life-threatening infectious conditions such as sepsis can only be reliably diagnosed using costly, time-consuming tests in an analysis laboratory with qualified professionals. Alternatively, functionalized magnetic nanoparticles can be used to considerably simplify the diagnostic process. To demonstrate the overall benefit, Fraunhofer scientists are developing an innovative system for quick, easy-to-use, and cost-effective on-site diagnosis of infections.

This system is based on magnetic particles. Depending on the application, they can be functionalized to act as carriers for proteins (e.g. antibodies), peptides, or disease-associated DNA sequences. These magnetic particles are deployed on a disposable resembling a credit card ("lab on a chip"). For on-site diagnosis, a sample (e.g. blood, saliva, or urine) is collected from the patient and introduced into the lab-on-a-chip system. After the target cells have been disrupted, the magnetic particles bind to the corresponding target molecules in the sample and, via magnetic forces, are transported through different reaction tubes in a fully automated manner. Besides highly sensitive magnetic sensors, optical and other methods are available for detection of the target molecules.

The combination of magnetic nanoparticles with pumpless microfluidics has generated a new diagnostic platform technology. This method can be adapted for a wide range of molecular biological challenges – from genetic predispositions via infectious diseases to cancer diagnosis.

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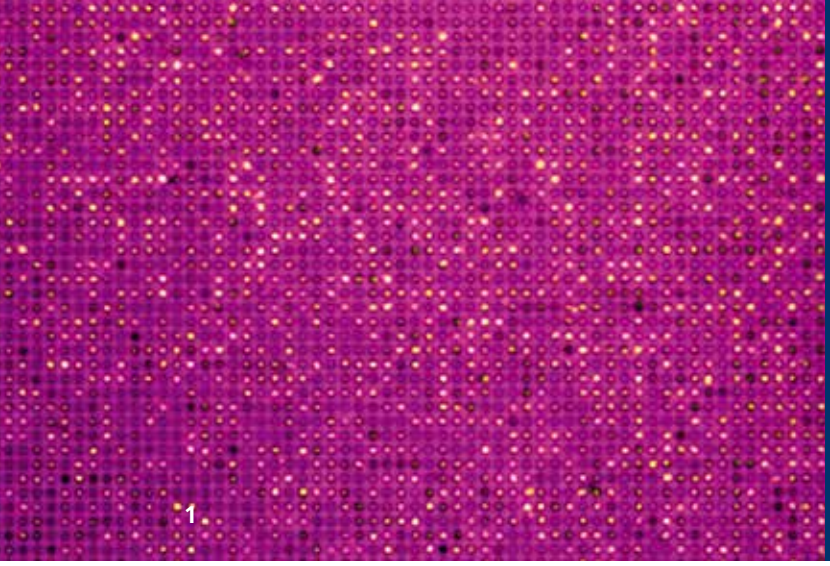
Nanoelectrodes for biosensors

Biosensors are key elements of medical diagnostics and in bioanalytics. They are the actual interfaces between biochemical-medical events and analytical tools. Improving these interfaces is crucial to opening up new applications for bioanalytical methods, which are determined, among other factors, by their detection sensitivity, geometric size and cost of the nanoelectrodes. To this end, Fraunhofer scientists are developing biosensors of sizes as low as in the nanometer range, which can be specifically functionalized using novel methods. This is done in close cooperation with partners from the pharmaceutical industry to enable in particular detection of biomarkers that are of medical interest, and with semiconductor manufacturers in order to reach the necessary miniaturization.



1 *Field-based immobilization of antibodies: fluorescence microscopic image using false-color representation; yellow: antibodies, purple: electrodes.*

The same microstructuring technology that is established in the semiconductor industry is used to produce measuring electrodes which are so small that arrays of even more than ten such electrodes fit on the surface of a single blood cell. The manufacturing process also allows the evaluation electronics to be integrated on the same chip. This results, on the one hand, in increased reliability of the complete system and, on the other hand, in substantial cost reductions, that is, effects that have been known from the electronics sector for years.

To endow these electrodes with specificity, that is, to make them sensitive to certain – medically relevant – substances, they must be equipped with detection structures. These can be, for example, antibodies or enzymes which usually are bound to the surface with chemical methods. In the Fraunhofer Group for Life Sciences, electric fields are preferably used to systematically bind such detection molecules to the electrode surface. This method has been used for quite some time already for characterization and sorting of living cells. Manipulation of nano-objects such as viruses or even dissolved molecules is principally also possible, however, this requires the characteristic dimensions of the electrodes to be also in the nanometer range. Given that the manufacturing of such electrodes so far has been a complex process, only few institutions worldwide are able to move such nano-objects systematically via a purely electric control and to immobilize them without any chemical intervention. Due to the development of special structures, we now have nanoelectrodes available that can be manufactured inexpensively using standard lithographic methods. A benefit of the field-based method is the fact that molecules can be bound specifically to the electrodes only, allowing high concentrations on the electrode surfaces and at the same time relatively low concentrations in the liquid to be reached. It has been demonstrated that antibodies and enzymes adhere to the surface of the electrodes without any additional chemical agents or reaction steps. This results in a faster production process and reduced costs.

The functionality of the electrode arrays that can meanwhile be reached should enable simultaneous testing of even complex samples for several substances at once. This can be achieved by actuating and reading out each electrode individually. Given their small size, also in comparison with living biological cells, multiparameter analysis of single cells thus seems possible. Work is underway to integrate the electronics both for field generation and for detection on the chip.

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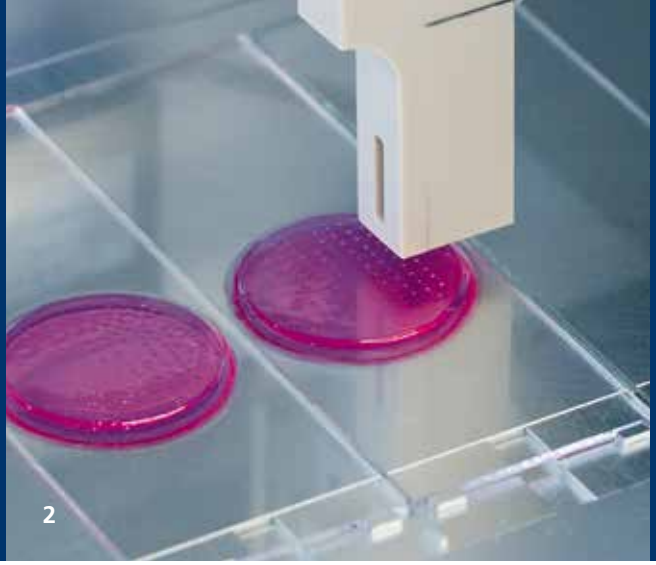
2 *Bio-ink laden with living cells is printed onto hydrogel pads.*



Bio-ink of living cells for tissue engineering

By developing biofunctional inks, the Fraunhofer Group for Life Sciences is pursuing a new approach to produce functional structures and matrices for medical and tissue engineering. The aim is to load these inks with human cells and then print them.

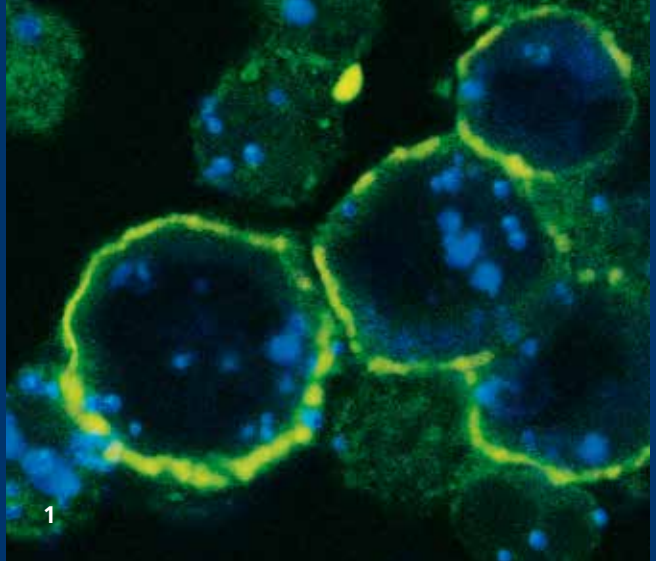
Biofunctional inks

The ink solution consists either of biological components of the extracellular matrix (the natural cell environment) or of cell-compatible synthetic molecules. Encapsulation of cells in the biological inks can be based, for example, on gelatin. As a degradation product of collagen, which is the main component of natural tissue matrices, gelatin is a bio-artificial matrix that is very similar to the natural original. In order to obtain fluid, printable inks that do not cross-link to form stable hydrogels until after printing, the Fraunhofer scientists modify the biopolymers at the molecular level. If UV-linkable functionality is introduced, curing to hydrogels can be triggered by UV irradiation. The gelling behavior and viscosity of the ink solutions and also the strength and swelling characteristics of the resulting gel can thus be controlled. This allows the characteristics of natural tissue to be mimicked – from solid cartilage to soft fatty tissue. After curing of the matrix, the cells incorporated in the bio-ink thus find themselves in a natural environment, supporting the self-organizing behavior of the printed cells to form a functional tissue model. Alternatively, using synthetic raw materials such as multifunctional polyethylene glycols (PEG), the printers of the Fraunhofer Group can also produce gels promoting cell adhesion and with cytocompatible properties. For example, the Fraunhofer researchers have developed a PEG-based material system that cures to a hydrogel devoid of any by-products (click chemistry) and can directly be colonized with cells.

Artificial vascular structures

A key challenge in tissue engineering is to produce vascularized tissue that has its own system of blood vessels to supply the tissue with nutrients. This vascularization step is crucial to enable production of larger tissue structures in the future. The BioRap® technology, developed cooperatively by the Fraunhofer institutes IAP, IGB, ILT, IPA, and IWM, uses a combination of additive production methods, biocompatible and bio-based materials, and modeling and simulation according to biomimetic design principles. The core element is a production technology (patent pending) that allows the combined use of 3D inkjet printing and laser-based polymerization technology to create structures from biological and biocompatible materials that were previously designed on a computer. Material development is focused on the creation of cell-friendly materials and integration of functions such as controllable

1 *Delivery of nanoparticle-encapsulated anticancer drugs to tumor cells.*



elasticity. To colonize the synthetic materials with cells, biopolymers such as heparin, growth factors, or anchor peptides such as the amino acid sequence arginine – glycine – asparagine acid (RGD) are first chemically modified by the Fraunhofer scientists and then linked to the synthetic materials. In special bioreactors, a confluent cell layer then forms by adhesion of human cells to these bio-active components.

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Nanoparticles as drug delivery systems – pre-clinical tests

A chemotherapy treatment which affects the tumor but does not damage healthy tissue is one of the primary goals of cancer research. Scientists in the Fraunhofer Group for Life Sciences are studying nanoparticles for tumor therapy and are investigating their potential therapeutic effect in pre-clinical tests. Which nanoparticulate formulations can transport drugs specifically to tumor tissue? Are nanoparticles capable of funneling drugs through highly selective biological barriers such as the blood-brain barrier or the gastro-intestinal barrier? These are just two of the many questions we are trying to answer.

The experts in the Fraunhofer Group for Life Sciences are testing countless variants of nanoparticles loaded with active components such as cytostatic agents, photosensitizers, and siRNA. In addition, the particles are equipped with surface ligands. The ligands serve as a kind of navigation system. They recognize receptors that are overexpressed on tumor cells and bind specifically to them.

Using flow cytometry and confocal laser scanning microscopy, we are investigating cell cultures to explore the kinetics of cellular uptake and accumulation of the loaded particles as well as their distribution within individual cells. We subsequently analyze the degradation of the particles, the release of the active substance, and its biological efficacy.

In our studies we have shown that functionalized nanoparticles can be systematically directed towards target cells and that, in contrast to unmodified formulations, they only accumulate in the target cells, where the cytostatic agent is then released. This is another important step towards targeted chemotherapy.

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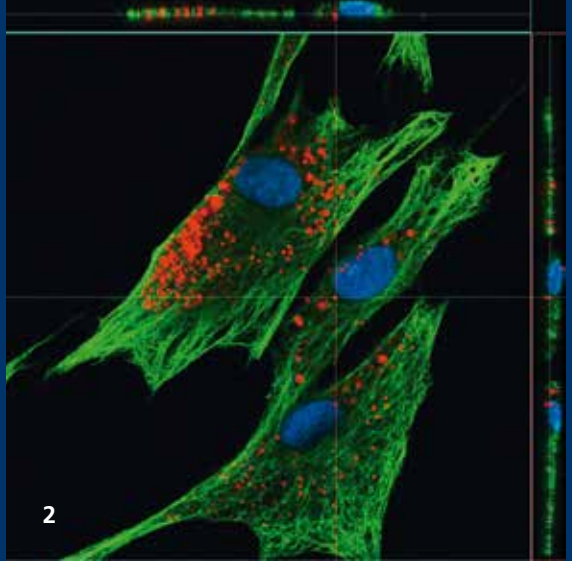

2

2 *Distribution of nanoparticle aggregates (red) in adult stem cells (green).*

Use of nanoparticles for cell marking and tracking of adult stem cells

The precise mechanism of action of stem cells in successful tissue regeneration is not yet fully understood. Stem cells from bone marrow are already in clinical use: they are injected into the heart to treat heart failure. Despite very positive results in numerous patients treated with this method, it is still not clear whether the transplanted cells remain in the heart muscle and differentiate to cardiomyocytes or whether they promote regeneration by releasing growth factors as paracrine mediators.

For detailed analysis of the fate and behavior of stem cells in the target organ, the cells have to be marked to enable cell tracking. First experiments in animal models have used genetically engineered cells that produce an artificial fluorescence protein (e.g. green fluorescent protein from jellyfish). These molecular biological methods are technically demanding and costly, and there is a need for cheaper alternatives that are easier to use.

Fluorescent nanoparticles such as quantum dots are opening up new possibilities here. They are passively taken up by cells and can accumulate in the cytoplasm as fluorescent aggregates. In a wide range of analyses, Fraunhofer scientists have tested the usability of quantum dot-based cell marking for adult stem cells. To preserve the stem cell characteristics, it must be guaranteed that the incorporated nanoparticles have no negative impact on cell proliferation, cell cycle, and differentiation potential. It has already been demonstrated that QTracker 605 nanoparticles can be used without problems as cell markers for pancreatic stem cells (Danner et al., 2013). Using time-lapse microscopy, it is even possible to watch the distribution of nanoparticles within the cell and their migration during cell division. Further evaluations are being performed in different organ culture models and animal models of cell-based therapies, to get also insight into the in-vivo behavior of such nanoparticles.

We have at our disposal a wide spectrum of cell technological and molecular biological methods to analyze the behavior of different nanoparticles in stem and progenitor cells and to test their usability for cell tracking.

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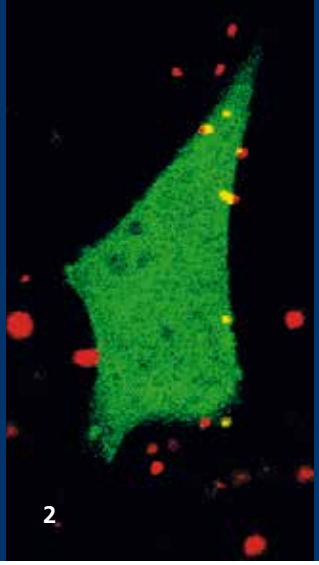
Reference: S. Danner, H. Benzin, T. Vollbrandt, J. Oder, A. Richter, and C. Kruse. "Quantum Dots Do Not Alter the Differentiation Potential of Pancreatic Stem Cells and Are Distributed Randomly among Daughter Cells". International Journal of Cell Biology, Volume 2013, Article ID 918242, 12 pages, 2013. doi: 10.1155/2013/918242



1 *Biodegradable nanoparticles.*

2 *Functionalized nanoparticles (red) docking to a target cell (green).*

Nanoparticles as components of contrast media

Fraunhofer scientists in the "Biomedical Ultrasound Research" group are investigating the possibility of using nanoparticles as contrast media for photoacoustic imaging. This imaging technique generates the measurement signal by transforming light energy to thermal energy and finally to pressure. Photoacoustic imaging uses nanoparticles which strongly absorb light in the visible and near-infrared regions of the optical spectrum.

With the help of functionalized nanoparticles, photoacoustic imaging could provide information about molecular-biological changes in the target tissue (molecular imaging). This would require nanoparticles to accumulate in selected tissues or cell structures and to absorb light there within a defined spectrum.

First successful results have already been achieved. The Fraunhofer scientists have developed photoacoustic imaging systems for high-resolution visualization of particle clusters in cell cultures and for highly sensitive in-vivo detection of particles in a small-animal model. With regard to particle synthesis, the focus of research is on the production of biologically absorbable nanoparticles with defined absorption characteristics in a spectral range between 600 and 1100 nanometers.

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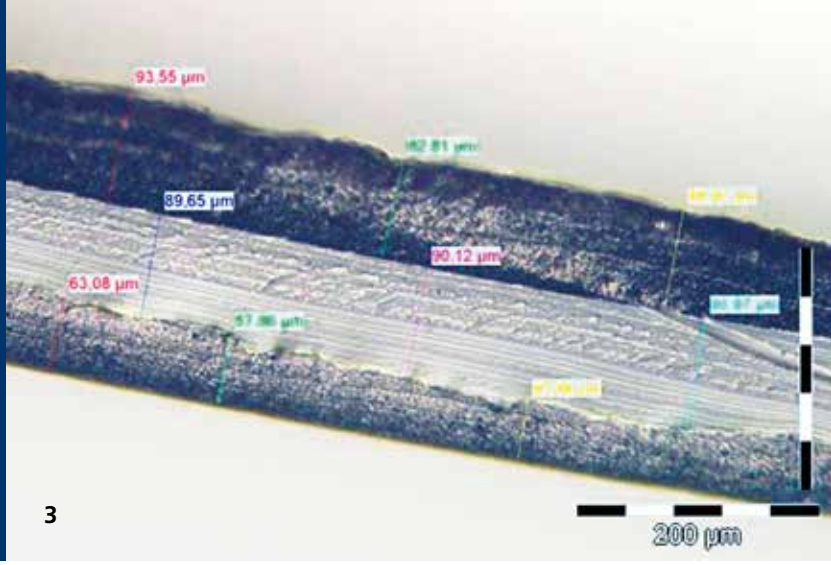
Implantable, elastic, nanofunctionalized polysiloxane structures

Implantable microsystems for the interaction with the human body play a crucial role in neuroprosthetics. Besides the components for signal generation, conditioning, processing, and transfer, sensory, actuatory, and bioactive components are of particular importance in this context. Utilization of flexible structures is desirable for numerous applications, because of their better mechanical compatibility with tissue. Systemic functionalization of polysiloxane (such as PDMS) with nanomaterials creates a novel material class for neuroprosthetics that is being evaluated and implemented in the basic scientific research project elaN.

The main goal of this project is to optimize the sensory and actuatory functionality of the interface between the biological system and the technical microsystem by means of nano-scale effects. This includes sustained improvement of the interface's performance and in particular the development of electric, mechanical, and bioactive interface functionality using materials of a single material class. Furthermore, a major benefit for the development of sensors and actuators for neuroprosthetics is the fact that the availability of a functionalized polysiloxane enables a monolithic structure of active system components made of a single material.

3 *Three-layer structure of a silicone-based electro-active polymer (EAP).*



3

Mechanical actuators

Hollow structures were developed from PDMS which allow targeted movements by generating low-pressure conditions. For example, for a finger with a chamber volume of 12.3 ml, a 66-degree flexion with a grip strength of 9.2 N and a mean speed of 0.04 m/s could be achieved. Great potential as intra-operative support system or to improve the contact between electrodes and nerves is seen in this technology. Silicone-embedded shape-memory materials are another approach.

Thermoelastic silicones that shrink under heat and electro-active polymers (EAPs) that change their shape without a change in volume upon application of electric current have only low potential as implants at present, because of their high energy requirements. EAPs consist of an elastomer (PDMS) located between two flexible, conductive silicone layers (see figure 3).

Bioactive actuators

In the elaN project, a composite material made of the silicone PDMS and a hydrogel has been developed (see figure 1 on page 14). The high proportion of hydrogel on the one hand improves its biocompatibility as a silicone-based implant material; on the other hand, the "interpenetrating network" of this composite allows diffusion of aqueous molecules such as hydrophilic active agents through the silicone. The substance release process can be influenced by integration of substances bound to micro- and nanoparticles, adjustment of the pore size within the composite and of the number of pores on its surface.

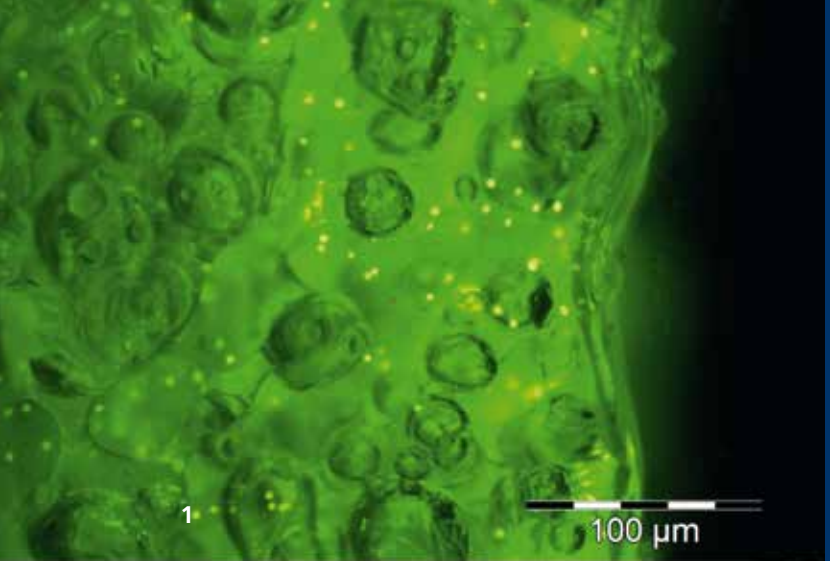
Furthermore, a method for immobilizing living cells in the PDMS-hydrogel composite has been developed. This allows cells releasing active pharmacological agents to be integrated into implant coatings, thus ensuring long-term improvement of implant integration into the body by "biologicalization" of silicone.

Electric actuators

Conduct of electricity in intrinsically conductive polymers can take place along polymer chains, but also via tunneling processes between chains. If polymers are filled with particles such as carbon black, carbon nanotubes, or silver, their conductivity is based on formation of a percolation network between the individual particles. Electrodes produced in this way can be used both for signal excitation and signal acquisition.

Mechanical sensors

Using the replica-molding method, test structures were generated and the electromechanical characteristics of filled polymer structures were determined. Strain-dependent resistance can be classified into three major categories: (1) proportional relationship, (2) inversely proportional relationship between strain and resistance, and (3) constant resistance with changing strain. These three categories allow mechanical sensors to be tailored to a specific application.



1 *Fluorescent L929 cells immobilized in a PDMS-hydrogel composite.*

Electric sensors

Successful tests have demonstrated that it is possible to construct electrodes for signal acquisition using conductive PDMS structures. Bioelectric signals of different geneses can be captured without problems. Studies on the electromechanical characteristics of conductive polymers have shown that the strength of the strain-dependent effects depends on the kind of particle integrated. For example, the electrical resistance of a polymer filled with carbon nanotubes can be considered strain-independent, if the strain is of a low degree.

Scientific and economic expandability

The results obtained in this project for polysiloxane-based actuators and sensors are applicable to any kind of implant. For example, besides their suitability as drug delivery systems, PDMS-hydrogel composites can generally be used for capsulation of implants, so as to increase their biocompatibility. In contrast, nanoparticles filled with polysiloxane have the potential to provide a flexible and monolithic basis for actuatorily and sensorily active materials. All in all, the insights gained in this project thus contribute to the existing knowledge in process technology, manufacturing, and quality assurance in the field of medical engineering.

Utilization of the insights and results from this project for future use in neuroprosthetics and medical engineering, also in cooperation with industry partners, is thus possible. This provides good chances for further exploitation beyond this project.

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2 *Nanotechnology enables shorter cycle times in the injection molding process for bottles and faster stretch blow molding processes.*

Nanotechnology in food packaging

Fraunhofer scientists view the food production chain – from initial production via processing, packaging, and distribution right through to the consumer – as an integral process. In our opinion, food packaging is one of the decisive factors for ensuring food quality and food safety. The packaging not only protects the food from germs such as molds, it also prevents unwanted interactions such as oxidation in the presence of light and oxygen.

The more sensitive the goods, the higher are the demands on the packaging material. Mass-produced plastics often prove to be inadequate here. With nanoparticles, however, it is possible to functionalize packaging materials, giving them additional characteristics. For the packaging industry, interesting options for using nanoparticles are as fillers in varnishes and polymers, as nanocomposites, and as coatings. An example: a layer of only 20 to 30 nanometers of an inorganic material applied by vapor deposition allows the barrier function of polymer films against gases and vapors to be substantially improved – even if the packaging has to be transparent.

Nano-scale modifications can also be achieved with plasma-based technologies. We systematically vary the process chemistry and process parameters in order to functionalize surfaces according to the client's requirements. We can influence different characteristics such as scratch resistance or modify the interface properties with regard to surface energy.

Our clients also benefit from the addition of carbon nanotubes (CNTs) to thermoplastic materials. The results are shorter cycle times in the injection molding process for bottles and faster stretch blow molding processes due to improved IR absorption and heat conduction. The Fraunhofer Group for Life Sciences is exploring appropriate concepts and the possibility of producing packaging films based on this approach. In addition, we test and assess the properties of such innovative packaging solutions.

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1 *Sustainability.*

RESEARCH TO REDUCE CONSUMPTION OF LIMITED RESOURCES

Nanomaterials have great potential for reducing the burden on the environment. Nanotechnology and the resulting products make it possible to use scarce raw materials and energy more efficiently. This may help reduce the consumption of resources and the emission of pollutants and carbon dioxide. In addition, nanotechnology plays an important role in the development of alternative energy sources – a topic of great ecological relevance.

The great potential of nanotechnology for reducing the burden on the environment can be brought to bear in widely differing products:

– More efficient batteries with nanocomposite membranes
– Photovoltaic cells with a higher degree of efficiency
– Nano-scale powders enabling chemical production processes at lower temperature
– Polymer nanocomposites, e.g. for light-weight construction materials
– Nano-scale photocatalysts to replace disinfectants
– Nanoporous thermal insulation materials for buildings

Nanotechnology also enables more efficient use of energy and resources in conventional production processes (nanotechnology for production, sustainable production). Nanomaterials and nanotechnologies thus contribute to energy storage, efficient use of energy and resources, and protection of the environment.

Almost one third of all the institutes in the Fraunhofer-Gesellschaft are engaged in nanotechnology. They have pooled their scientific expertise in the Fraunhofer Nanotechnology Alliance, which is focusing its research activities on the following key areas:

– Multifunctional layers for surface finishing (protection against corrosion, tribology, barrier functions, easy-to-clean coatings)
– Design and production of special nanoparticles for use in biotechnology, medicine, optics, plastics technology, and wastewater treatment
– Use of carbon nanotubes in composites, e.g. for actuator applications

For further information, please refer to: www.nano.fraunhofer.de

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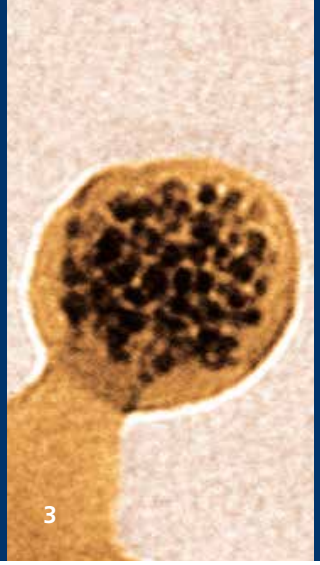

2 *Nanostructured adsorber for water treatment.*

3 *Nanoparticle with magnetizable core.*

Specific removal of environmental pollutants

Active pharmaceutical ingredients are important in our fight against illness and disease, but we certainly would not want to see them in our drinking water. There are different ways in which these substances can get into the environment. The main pathway is via humans, either excreting residues of the medication they have taken or flushing unused portions down the toilet or drain.

Many drugs, however, are not or only partially degraded, even in biological sewage plants. Liposoluble pharmaceuticals may accumulate in the environment (bioaccumulation); water-soluble substances bind poorly to sediments and thus travel from contaminated surface waters as far as into the groundwater. Over 100 different active pharmaceutical ingredients have so far been identified in the aquatic cycle – some of them at concentrations above the ecotoxicological threshold values. Degradation of these substances via physicochemical processes such as ozonolysis or adsorption on activated carbon is either very costly or the process itself produces toxic degradation products.

We are therefore pursuing a completely new approach: we are removing the pollutants using specific adsorbers produced from nanostructured plastics. During the manufacturing process the plastic beads are provided with a biofunctional surface. Using this patented process, the polymeric materials are prepared in a nanostructured fashion as selective adsorbers for specific molecules and molecule groups. The water-based manufacturing process we use for this creates selective molecular recognition sites in the polymers. The microstructure or nanostructure of the particle surface remains after the manufacturing process.

Among the most prevalent micropollutants are pharmaceuticals such as analgesics/anti-inflammatory drugs, anticonvulsants, and beta blockers. We have developed nanostructured and microstructured specific polymeric adsorbers (SPAs) which can be used to selectively remove the active agents diclofenac and pentoxifylline from wastewater. In a model, we were able to adsorb up to 500 micrograms of pentoxifylline in one gram of the NanoMIPs (nanoscopic molecularly imprinted polymers). Pentoxifylline has been classified in the highest water pollution class, namely it is considered to be "severely hazardous to water".

Furthermore, we were successful in removing bisphenols and antibiotics from water using specific adsorber polymer particles incorporated into membranes. It is also possible to give the beads a magnetizable core to allow adsorber particles – together with the adsorbed pharmaceuticals – to be trapped using a magnetic separator.

In particular for organizations producing large amounts of micropollutants – such as hospitals – such polymer beads may help minimize pollution or even prevent such pollutants from being introduced into the water cycle via contaminated wastewater.

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OPPORTUNITIES RESULTING FROM PREVENTION

1 *Freshly ground quartz.*

2 *Bronchiole with cilia and secretion cells.*

NANOTOXICOLOGY – POTENTIAL HAZARDS FROM SYNTHETIC PARTICLES

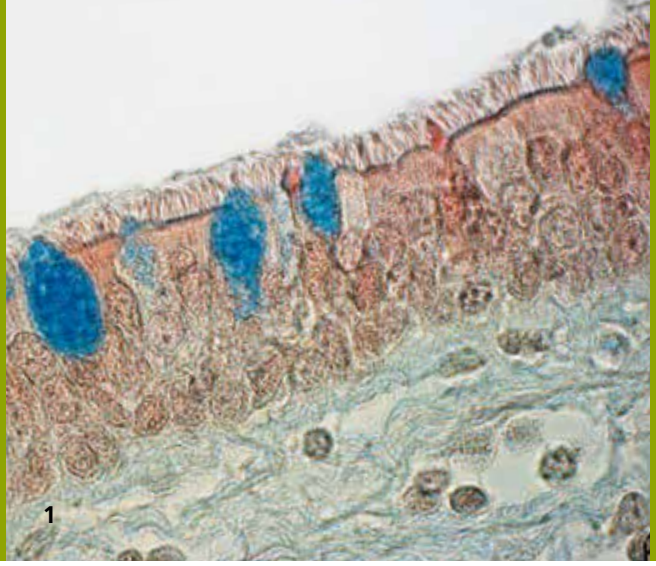
A high degree of safety in the field of nanotechnology can be achieved by carrying out exposure analyses and hazard assessments and by developing preventive recommendations. Potential risks can thus be minimized and controlled, meaning that the chances of bringing to bear nanotechnological developments are substantially enhanced. The important contribution provided by research organizations makes it possible for industry to establish itself in many application areas, so further expanding the potential uses of nanotechnology.

What happens to nanoparticles when they enter the human body or the environment? Researchers in the Fraunhofer Group for Life Sciences are also investigating the potential hazards of nanomaterials. Possible interactions between nanoparticles and living organisms have to be studied with an enhanced range of endpoints, because nanoparticles and particles in the micrometer range differ in their biological effects. This observation seems to be based on differences in their physicochemical properties and the subcellular size of nanoparticles. In parallel with nanotechnology, a new scientific discipline has therefore evolved: the toxicology of nanomaterials.

An important aspect of nanotoxicity research is extrapolation of results obtained in laboratory experiments to humans. Well-founded conclusions in the area of nanotoxicity require not only animal models, but also human cell systems, i.e. cell- and tissue-based in-vitro test systems. Primary cells from different organs are ideal for this purpose. Their availability, however, is limited, and the partly commercially available cell lines that are used instead of primary cells differ substantially from their presumed equivalents in the human organism – even though initially they were of human origin. This is why we are investigating and developing novel test systems, placing the focus on guaranteed extrapolability of the results to man.

For hazard assessment of chemicals and pharmaceuticals there are standardized and accepted in-vitro test methods capable of providing reliable data for initial hazard analysis at an early stage of the testing. For nanomaterials the situation is totally different: this group of materials is defined primarily by its dimensions. A glance at the literature reveals a large variety of incongruent data for the results of toxicity tests. There are still substantial gaps in current knowledge and methodological deficiencies in the assessment of potential hazards to human health. In the Fraunhofer Group for Life Sciences, one approach we are pursuing with regard to toxicity screening is, therefore, the development and validation of in-vitro tests in parallel to in-vivo experiments.

Existing in-vitro approaches at present primarily focus on the mechanisms of action of these materials. Using potential human target tissue, these are already used today to complement toxicological investigations of nanomaterials in animal models.



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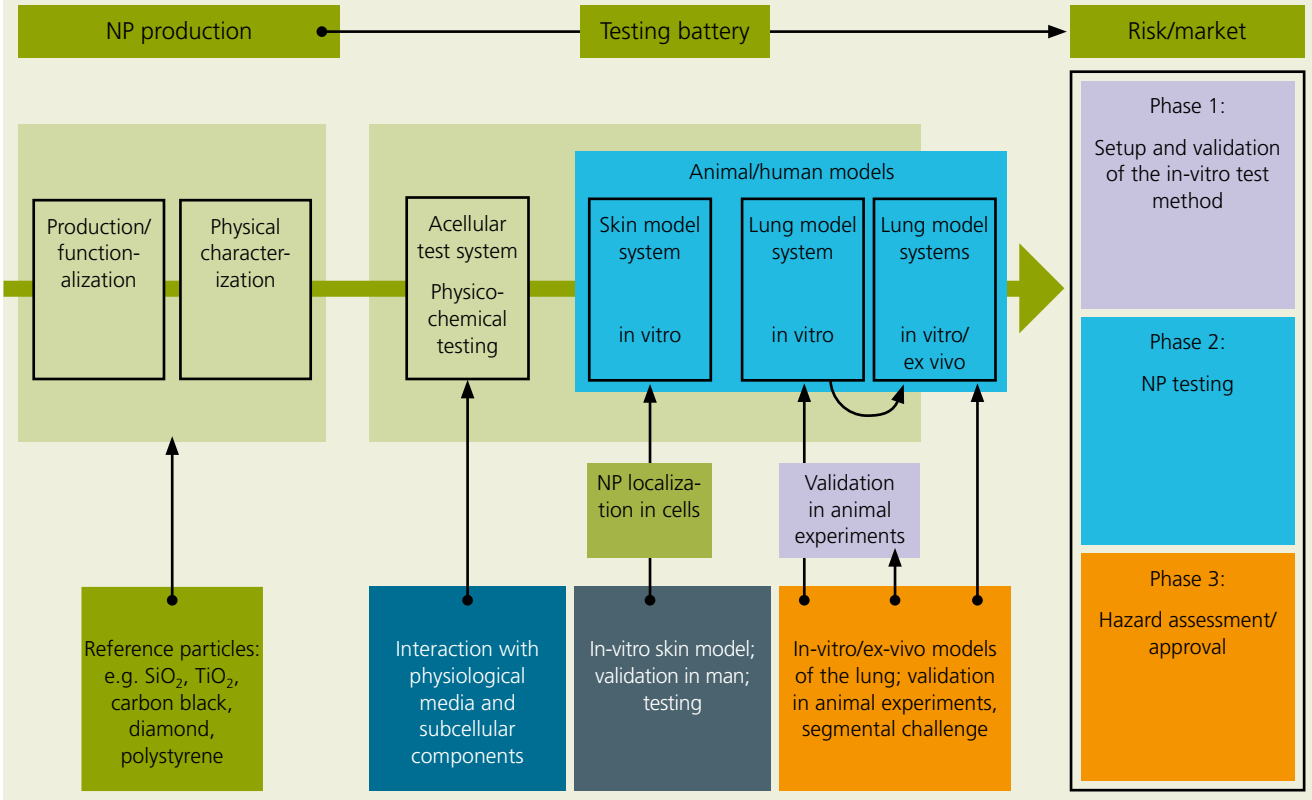
An appropriate approach for screening novel nanomaterials for their potential toxicity is the procedure outlined in the below figure, which provides for testing of nanomaterials by means of in-vitro assays after comprehensive physicochemical characterization. The decisive point here is that these in-vitro assays have been validated by means of in-vivo assays performed in parallel.

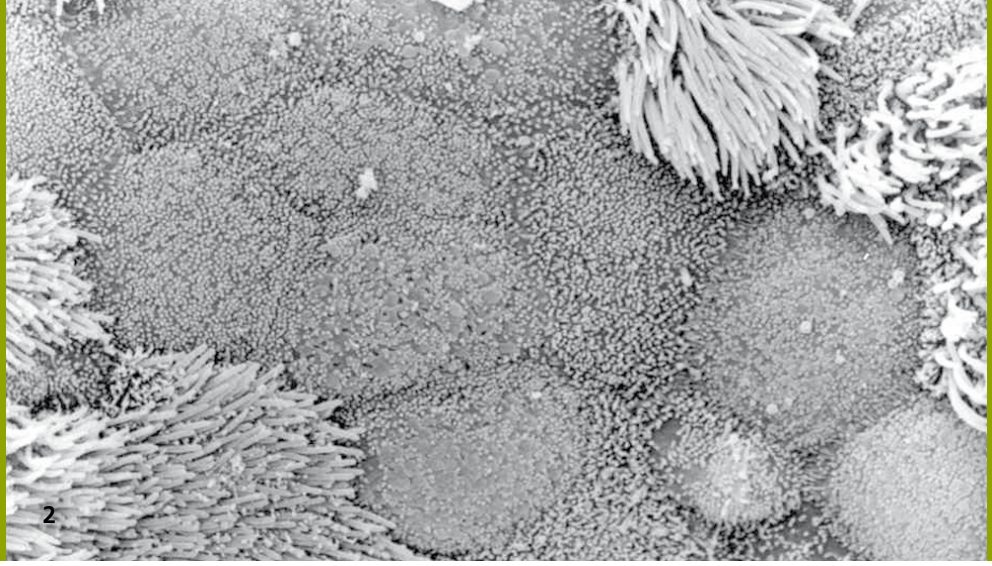
The exposure risk from nanoparticles concerns the following pathways (with decreasing priority): inhalation, dermal exposure, and ingestion (stomach and intestines). Accordingly, the assays established in the Fraunhofer Group for Life Sciences will be presented here in the following order:

– Uptake by inhalation
– Dermal and oral exposure pathways
– Mechanistic and fundamental assays

Schematic approach for the establishment of validated in-vitro assays for nanomaterial and nanoparticle (NP) toxicity screening



Scheme adapted from Oberdörster G. et al., Particle and Fibre Toxicology 2005, 2: 8. doi: 10.1186/1743-8977-2-8



1 *Microscopic section through the trachea.*

2 *Lung cells.*

Ex-vivo and in-vitro inhalation toxicology research

The scientists of the Fraunhofer Group for Life Sciences have many years of experience in studying the cytotoxic and genotoxic effects of fibers, particles, and dusts. For regulatory purposes, the traditional GLP-compliant tests and cell models are used in accordance with the relevant guidelines, such as OECD guidelines. Other focuses are on the development of nanomaterial-adapted methods and on ex-vivo and in-vitro cell models tailored to the demands of the respiratory tract as target organ. Reliable and proven testing strategies are used to exclude any undue influence of the nanomaterials on the tests and the analytical setup. This is particularly important in the testing of carbon nanomaterials.

At present, projects investigating the biological effects and systemic availability of different fine particulates and nanomaterials (such as carbon black, carbon nanotubes, graphene platelets, and metal oxides) are being performed on behalf of clients from industry and public authorities (EU, German Federal Ministry of Education and Research, and German Federal Institute for Occupational Safety and Health) and in close cooperation with Fraunhofer inhalation toxicologists, aerosol technologists, pathologists, and with the Fraunhofer Nanotechnology Alliance. These studies are focused on the uptake of nanomaterials into target cells such as lung epithelial cells and alveolar macrophages, and on detection of subsequent damage to these cells depending on particle size, morphology, and surface. Endpoints which are known to be modified upon exposure to particulate matter and which can be analyzed in ex-vivo and in-vitro studies include release of reactive oxygen species, oxidative stress, inflammation, cytotoxicity, effects on cell cycle control and proliferation, altered cellular signaling pathways, modified gene expression, and genotoxicity. State-of-the-art imaging techniques, including ultrastructure analysis (REM/TEM) coupled with elemental analysis (EDX) and fluorescence microscopy in the dark-field mode with the additional possibility of hyperspectral analysis and transfer of samples to TEM analysis, allow also visual detection and identification of the test materials in cells and tissue.

Together with complementary data from in-vivo studies, the in-vitro data serve as basis for hazard and risk assessment of the investigated nanomaterials, which is performed by our experts in the field of chemical risk assessment.

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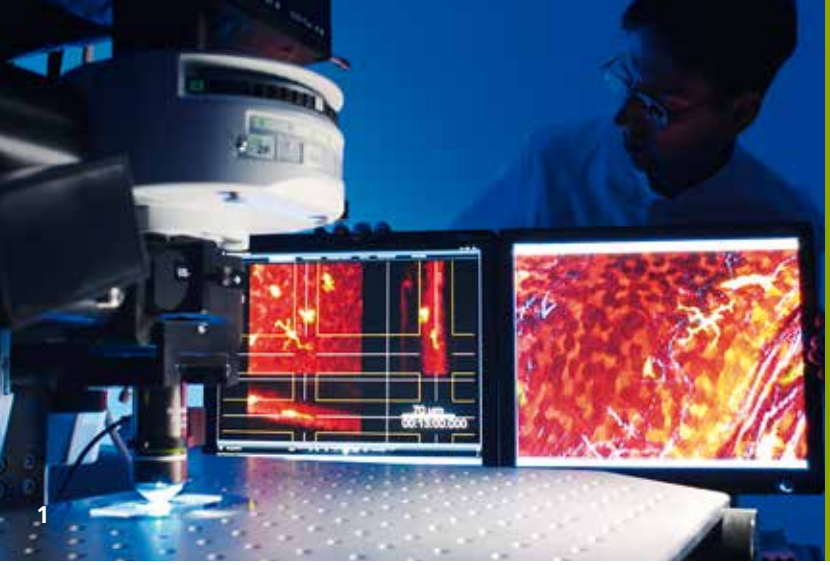

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In-vitro immunotoxicological assays

By means of a comprehensive spectrum of in-vitro assays we investigate the immunotoxicological effects of nanoparticles using established state-of-the-art methods. These include, for example, real-time RT-PCR according to the UPL principle, which we use for gene expression analysis of a broad range of immunologically relevant genes such as cytokines, chemokines, toll-like receptors, and others, or for flow cytometric analyses (immunophenotyping, intracellular staining of cytokines and phosphoepitopes).

In addition, the evaluated xCELLigence real-time cell analysis system means that we possess an innovative method for ultrasensitive analysis of the impact of nanoparticles on the function of adherent cells (macrophages, endothelial cells, and epithelial cells). This method is based on impedance measurements (GLP standard). The cells are placed on gold electrodes at the bottom of a 96-well plate. Changes at the sites of contact between the cell and the gold electrode, which may be caused by proliferation, movement, adherence strengthening, receptor activation, or cell death, result in a change in the impedance. This can be measured in real time as a cell index with extremely high time resolution.

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In-vitro and in-vivo immunotoxicological assays

Potential immunotoxic effects after nanoparticle deposition in the respiratory tract can be determined using in-vitro models (ex-vivo alveolar macrophages, commercially available cells from the respiratory tract). For this, cytokine concentrations, formation of oxygen radicals, or phagocyte performance are measured, and immunohistochemical methods are deployed. These tests are used in vitro for immunotoxicity screening or are often included in the final spectrum of assays to complement in-vivo inhalation tests in rodents.

Besides animal experiments, controlled studies in humans are also feasible. These are performed, for example, to investigate the effects of inhaled nanoparticles (carbon particles) on the severity of an allergic response (challenge with grass pollen). The background here is that epidemiological studies have shown an increased incidence of asthmatic symptoms in asthma patients after increased exposure to nanoparticles. Inflammatory cells and immunotoxicological parameters can be analyzed in lung lavage fluid isolated from lung segments.

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1 *Live cell monitoring.*

2 *Lung function measurement station.*

In-vivo inhalation toxicology research

Nanostructured particulate matter (agglomerates, aggregates) is taken up by the organism primarily by inhalation and deposition in the respiratory tract. Besides possible harmful effects in the lungs, nanoparticles have high penetration capacity and so have the potential to act systemically and induce damage even in distant organs or tissue.

The Fraunhofer Group for Life Sciences has a lot of experience investigating particle and fiber toxicity, for example, of ultrafine particulate matter such as amorphous SiO_2, TiO_2, and carbon black, as well as carbon nanotubes taken up by inhalation. The scientists have many years of experience generating respirable aerosols and investigating particle-related biological effects.

Important requirements in these investigations are the maintenance and documentation of well-defined aerosols for the whole duration of the exposure and the use of a broad, interdisciplinary range of endpoints. Inhalation tests are performed as collaborative projects involving different working groups and a combination of different endpoints such as clinical chemistry (changes in the blood, lung lavage), histopathology, chemical analysis of particle retention and translocation, as well as analyses by electron microscopy.

In order to also take into account special aspects of lung physiology, we investigate the interaction of lung surfactant, a special lining of the pulmonary alveoli, with nanostructured particles deposited in the lung. We study its role as a physiological barrier with regard to the uptake and transport of nanoparticles.

In addition, we actively collaborate in the OECD program on the nano-specific investigation of high-volume ultrafine particulates (ZnO, SiO_2, and TiO_2). The projects performed in this program are interdisciplinary, aimed at establishing validated test systems for the assessment of the toxic potential of nanoparticles and at closing data gaps.

In publicly funded studies with carbon nanotubes, we investigate the relevant morphological criteria that make a particular type of carbon nanotube a carcinogenic agent.

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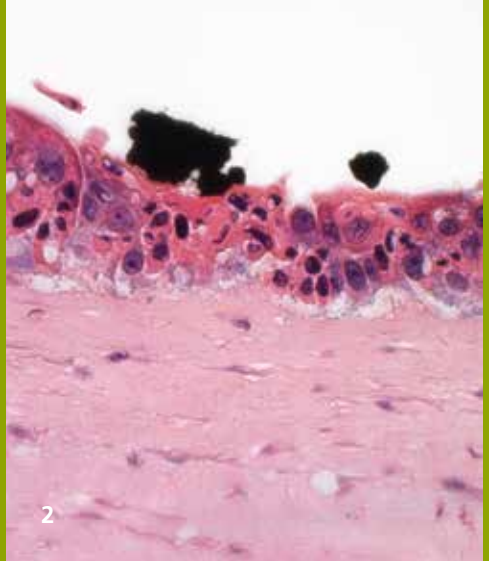

1 *Three-dimensional skin testing systems.*

2 *Skin model with deposited nanoparticles.*

Measuring ultrafine particles in the workplace

Inhalation of dust in the workplace can be a significant health hazard. This holds true in particular for ultrafine dust and nanoparticles. The current debate on occupational safety clearly suggests that ultrafine dust should be considered separately. In the majority of cases, however, ultrafine dust does not occur in an isolated state. It is normally masked by coarser particles and is only present at low mass concentrations. Separate measurement of the exposure to ultrafine particles and nanoparticles is therefore difficult.

In the Fraunhofer Group for Life Sciences a new sampler has been developed, called the "Hybrid Aerosol Classifier". It is a small personal sampler weighing only 50 grams which enables differentiated measurement of inhalable dust. The dust can be analyzed separately in five health-relevant particle size ranges. The important lowest size range for particles below 100 nanometers has a special feature: four partial streams of the ultrafine fraction can each be diluted by a different factor and passed through a filter segment. The deposits can subsequently be analyzed in a differentiated manner.

In the design and construction of the device, great importance was attached to quickness and ease of use. It can be operated without difficulty during a complete work shift.

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In-vitro skin and trachea test systems

In-vitro tests with cell cultures are only relevant for cytotoxicity assessment of nanomaterials, if it can be demonstrated that nanoparticles overcome the body's barriers (penetration), are distributed via the bloodstream (resorption), and are thus able to reach the body's organs. We, therefore, use different test systems (including vascularized systems) such as skin and trachea to study the penetration and resorption behavior of nanomaterials. Emphasis is always placed on physiological cell culturing, so as to mimic the body's barriers in vitro close to the natural situation. The skin model thus allows analysis of particle penetration through the stratum corneum and the epidermis into the blood circuit. A trachea model is also available, which we use to investigate how particles affect the cells of the upper airways, once they have been inhaled.

Using these three-dimensional models, we are well qualified to investigate and answer your questions about the biocompatibility and toxicity of a wide range of different materials – regardless of whether these are aerosols, liquids, or solid substances.

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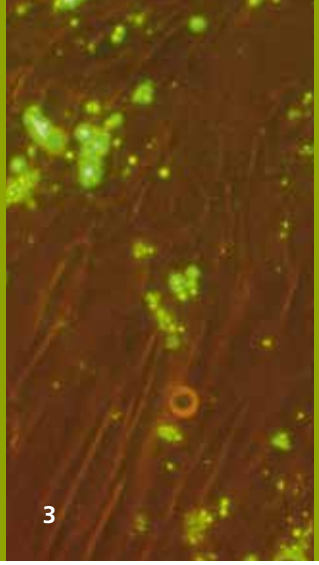
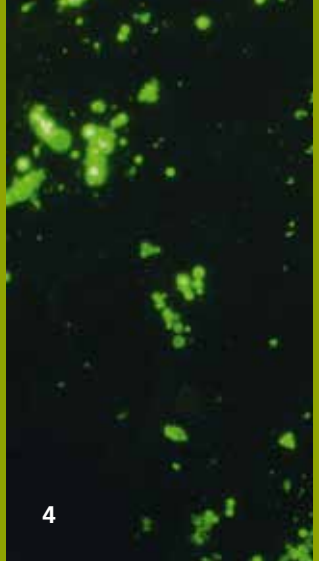
3, 4 *Pancreatic stem cells – the uptake of nanoparticles differs between cell types.*





In-vitro test system with human adult stem cells

Due to their capability to differentiate into different cell types, human adult stem cells might allow the potential nanotoxicity of particles to nerve, muscle, epithelial, and many other cells to be studied. It is known that there are substantial differences in the uptake of nanoparticles depending on the cell type. This has also been demonstrated in a stem cell culture: some types of cells accumulate large amounts of nanoparticles, whereas others do not incorporate any particles at all.

Different parameters such as cell viability, adhesion behavior, proliferation behavior, and long-term survival can be investigated in adult stem cells by using common methods of cell and molecular biology. The aim is to provide relevant information that will enable the definition of guidelines ensuring maximum safety for those handling nanoparticles.

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Chip-based test systems for investigating nanoparticle-cell interactions

Biohybrid systems – a combination of biological cells with technical microsystems – are the basis for improved assay technologies. Cell-based test systems with increased sensitivity and reproducibility, information at the single-cell level, and long-term studies in vitro are then possible. Furthermore, we can determine not only whether there is a cellular effect, but can now also find out why cells respond in a particular way (mechanisms of action). This is important when products have to be optimized with regard to a certain biological effect. Tests can be performed with nanoparticles made of many different materials, such as biodegradable polymers, and inorganic and metal-based materials. Using our technologies, we offer services to develop devices, customized test systems, and support in the development of drugs, therapies, and materials.

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RESEARCH FOR ENVIRONMENTAL PROTECTION

Whether and how nanomaterials affect the environment cannot yet be sufficiently evaluated. We are of the opinion, therefore, that all actions should be governed by the precautionary principle and we are investigating in depth the potential environmental hazards of nanomaterials.

Effects and behavior of nano-objects in the environment

Environmental nanotechnology research is currently undergoing rapid development. The Fraunhofer Group for Life Sciences has had close contact with national (e.g. the German Federal Environment Agency UBA) and international authorities (e.g. OECD, EU) for many years. Our experts collaborate in relevant committees (e.g. OECD, ISO) and major national and international research programs of the German Federal Ministry of Education and Research, the German Federal Ministry for the Environment, and the European Union. We are thus able to guarantee that our research work always takes into account the most recent developments and findings in environmental research.

According to the ISO/TS 27687 definition, by "nano-objects" we understand materials that have at least one dimension in the size range of 1-100 nm. In order to characterize the environmental properties of free nano-objects and explore their potential effects on the environment we conduct experimental studies using test methods which are accepted by the authorities. The range of methods we employ covers standard tests based on international guidelines (e.g. OECD) and extends through to comprehensive studies on very complex issues. These may also be performed in compliance with REACH requirements. Studies under GLP conditions are the standard. Since meaningful simulation experiments, in particular, are often not standardized, we offer to design simulation experiments tailored to clients' specific problems and consult with the authorities in advance to ensure their acceptance.

Ecotoxicology of nano-objects

We possess expert knowledge in the following areas:
- Standard test methods required for ecotoxicological rating and classification of a material
- Long-term ecotoxicity studies
- Studies aimed at a refinement of the PNEC (predicted no-effect concentration), for realistic assessment of the hazard ratio
- Studies describing the effects in specific environmental compartments
- Application of nano-objects in aquatic and terrestrial ecotoxicity tests, taking into account potential interactions with the test media and possible alterations of the nano-objects and their agglomerates

We have a comprehensive range of methods which allow us to characterize the dispersion of nano-objects. The size distribution in agglomerates, measurement of the zeta potential, and differentiation between nano-objects and released ions (e.g. nano-silver) are only a few examples of possible analyses in this context. Thus, the relationship between environmental conditions and effects can be elucidated.

1 *Microcosm growth.*

2 *Lab-scale sewage treatment plant to simulate the environmental behavior and effects of nanomaterials.*

Test systems

In order to estimate the behavior of nano-objects in the environment, we measure a variety of relevant data and offer studies and simulations. These are based on methods originally developed for the testing of chemicals, but modified specifically to meet the special requirements of nano-object testing. This ensures good acceptance by the authorities, because they are already familiar with these test systems. In addition, however, we also develop customized solutions for specific problems and innovative test systems in close cooperation with the client and design object-specific testing strategies.

The 4F-analysis method, which currently represents the only possibility to analyze nano-objects in complex environmental matrices, in the future will enable evaluation of the mobility, behavior, and distribution of nano-objects in individual environmental compartments. Furthermore, carbon-based nano-objects can be tracked with the ^{14}C-tracer technology. It is the combination of complex chemical analytics and ecotoxicological testing that enables the establishment of dose-response relationships – which are crucial for risk assessment – and their application to soil, water bodies, and sewage treatment plants. In this context, we also study the materials' bioaccumulation potential in different organisms such as fish and earthworms, given that even small environmental concentrations can lead to unexpected effects through bioaccumulation.

Nano-objects as product constituents

Nanotechnology is used systematically to endow products with defined features. These include, for example, chemical or crystalline properties of nano-objects or their surfaces, which are implemented in product systems. For comparative demonstration of the photocatalytic activity of self-cleaning (easy-to-clean) surfaces or of air-cleaning surfaces, standardized methods have been established. The experts of the Group have been involved in this work. Examples are the photocatalytic degradation of air pollutants such as NOx (ISO 22197-1) and the detection of antibacterial activity (ISO 27447). For numerous other applications, no standard methods are available to provide evidence of their efficacy. We are able to simulate specific application areas and to offer functional tests having different degrees of complexity as well as practice-oriented simulation experiments, and customized tests. The strengths of a product and expected effects can thus be proven by an independent research institution, and unwanted side effects can be recognized in time and therefore eliminated.

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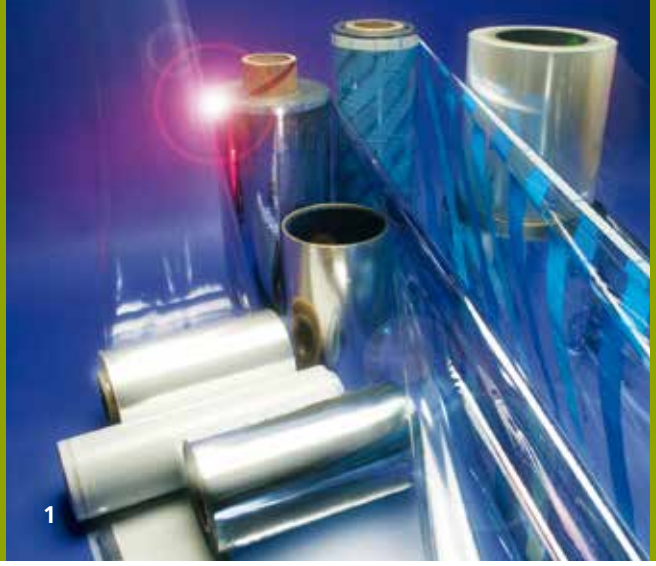

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PREVENTIVE TESTING OF INTELLIGENT PACKAGING SYSTEMS

According to the precautionary principle, Fraunhofer scientists are investigating whether nanoparticles can pass from nanoengineered packaging materials to the packaged food and are evaluating the potential hazards that might result from such a migration. As there are currently no data available in this area, the Fraunhofer Group for Life Sciences feels there is a substantial need for research and action here.

The decisive factor determining the migration potential of nanoparticles is the process by which the packaging material is functionalized. The following processing variants are possible:

Production of a multilayer composite by lamination
The sealing layer is connected with the nanoparticle-containing layer via a lamination process. As the adjacent layers are not thermally processed but are fixed with an additional laminating adhesive, migration of nanoparticles into the sealing layer is very unlikely.

Production of a multilayer composite by co-extrusion
No direct contact between nanoparticles and the packaged food should take place with this composite, but it cannot be strictly excluded. As this composite is produced by melt compounding, migration of nanoparticles into the layer in contact with the food is certainly possible during the melting phase.

Incorporation of nanoparticles into monolayer plastics
If monolayer polymers without sealing layers are mixed with nanoparticulate material, there will be direct contact with the packaged food. Migration of nanoparticles, therefore, is possible. The extent of the migration depends on the substrate as well as on the dimensions of the incorporated nanoparticles and on the processing conditions.

Internal coating with a nanomaterial
With this technology, direct contact between the packaged food and the nano-coating or nano-lacquer takes place. Migration of nano-scale fragments from this internal layer to the packaged food is possible.

1 *Functionalized packaging films.*

2 *Tailored packaging solutions for food.*

2

In the above-described variants, there is an increasing chance of nanoparticle migration. To enable analysis of nanoparticle migration processes from food packages we have developed test and measurement methods and can offer these to verify compliance with food regulations. The measurement method we use is asymmetric flow field-flow fractionation (AF4) coupled with MALS and/or ICP-MS detection.

We are focusing on answering the following questions:

- What nano-scale materials and substances are used for producing food packaging?
- Is it possible for nanoparticles to migrate from the packaging material to the packaged food?
- If so, under what conditions does migration take place and to what extent?
- What methods can be used to analyze these processes?

The work involves both experimental and theoretical approaches.

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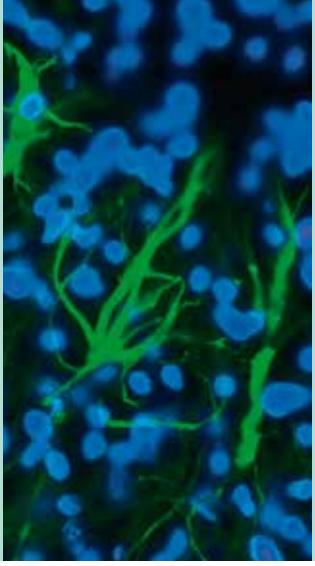
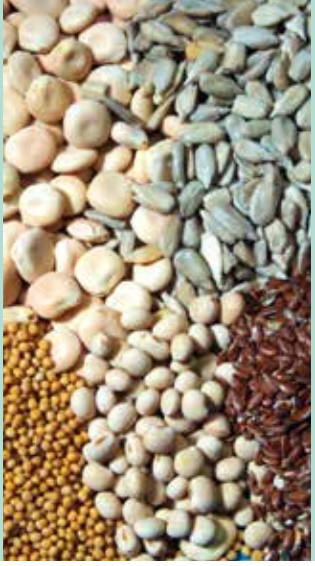



THE FRAUNHOFER GROUP FOR LIFE SCIENCES

The comprehensive and individually tailored services offered by the Fraunhofer Group for Life Sciences for the application of novel technologies require an organization that covers a broad range of disciplines, methods, and equipment. Under the motto "research for human health and the environment", the Fraunhofer Group for Life Sciences offers its clients a rich pool of complementary expertise.

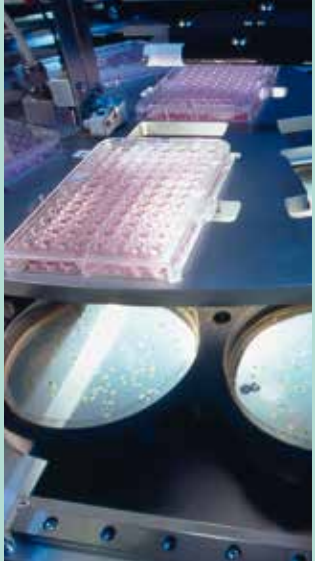
Six Fraunhofer institutes and a Fraunhofer research institution, each having proven in-depth expertise in different areas within the life sciences, are involved in this Group: the Fraunhofer institutes for Biomedical Engineering IBMT, Interfacial Engineering and Biotechnology IGB, Molecular Biology and Applied Ecology IME, Toxicology and Experimental Medicine ITEM, Process Engineering and Packaging IVV, Cell Therapy and Immunology IZI, and the Fraunhofer Research Institution for Marine Biotechnology EMB. Their combined knowledge of biology, chemistry, biochemistry, biotechnology, medicine, pharmacology, ecology, and nutritional science is thus pooled and synergized within this Fraunhofer Group. With the Fraunhofer EMB joining the Group in August 2012, marine biotechnology has become an additional focus. In all these Fraunhofer institutions, the scientists collaborate in interdisciplinary teams, so that tailored know-how concerning information technology, engineering science, and legal requirements is also available. Research and implementation at the client's facilities therefore go hand in hand.

The Fraunhofer-Gesellschaft stands for reliable partnership in applied research. As the largest research organization of its kind in Europe, it develops market-oriented solutions tailored to the specific requirements of each client. A solid basis for this is its own pre-competitive research, geared to the basics and frequently undertaken in close cooperation with universities and other academic institutions.

One of the most important things we have learned: the path from the very first idea to the perfect solution is always very exciting – and we will gladly go down this path with you.

Business units of the Fraunhofer Group for Life Sciences:

- **Medical Translational Research and Biomedical Technology:** The Challenge of Innovative Diagnostics and Personalized Therapy
- **Regenerative Medicine:** The Challenge of Qualified Biobanking and Controlled Self-Healing
- **Healthy Foods:** The Challenge of High Consumer Acceptance and Disease Prevention
- **The New Potential of Biotechnology:** The Challenge to Learn from Nature for Industrial Exploitation
- **Process, Chemical, and Pesticide Safety:** The Challenge of Environmental and Consumer Protection



Do you have any general questions regarding the Fraunhofer Group for Life Sciences, or any suggestions or requests?

Dr. Claus-Dieter Kroggel, Head of the Group's Central Office, will be pleased to assist you, so that you can quickly reach your goal.

Prof. Dr. Rainer Fischer
Chairman of the Fraunhofer Group for Life Sciences
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As of: February 2016

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