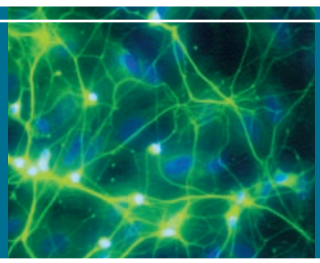
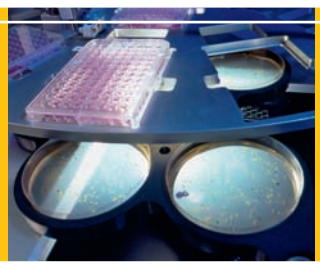
Fraunhofer
LIFE SCIENCES

FRAUNHOFER GROUP FOR LIFE SCIENCES

BUSINESS UNITS





CONTENT

1 *From left to right: Professor Frank Emmrich (IZI), Professor Uwe Heinrich (ITEM), Professor Horst-Christian Langowski (IVV), Professor Thomas Hirth (IGB), Professor Günter R. Fuhr (IBMT), Professor Rainer Fischer (IME)*

THE FRAUNHOFER GROUP FOR LIFE SCIENCES

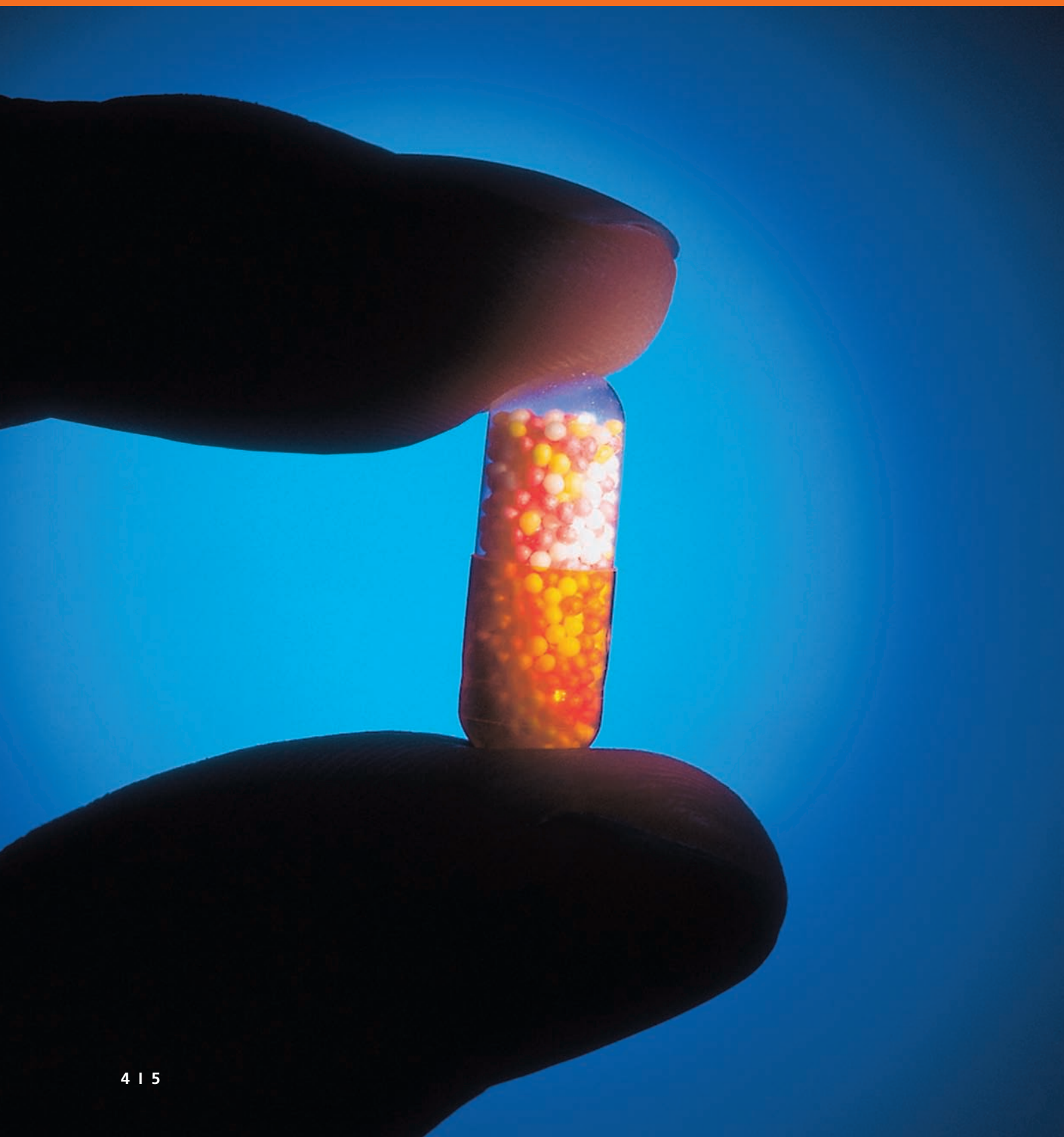
The comprehensive and individually tailored services offered by the Fraunhofer Group for Life Sciences for the application of novel technologies require an organization that covers a broad range of disciplines, methods, and equipment. Under the motto "research for human health and the environment", the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

Six Fraunhofer institutes, 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), and Cell Therapy and Immunology (IZI). Their combined knowledge of biology, chemistry, biochemistry, biotechnology, medicine, pharmacology, ecology, and nutritional science is thus pooled and synergized within this Fraunhofer Group. In all these Fraunhofer institutes, 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 preliminary 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.

MEDICAL TRANSLATIONAL RESEARCH AND BIOMEDICAL TECHNOLOGY: THE CHALLENGE OF INNOVATIVE DIAGNOSTICS AND PERSONALIZED THERAPY

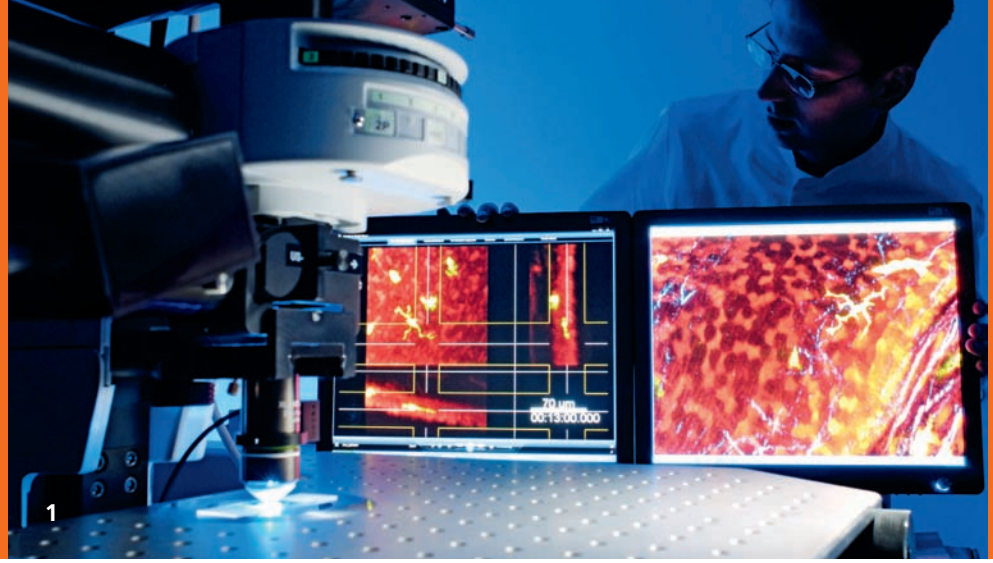


OVERVIEW

The therapeutic approaches for drug development and molecular genetics in the Fraunhofer Group for Life Sciences take into account the individual's genotypic profile. To enable quick interaction between basic research and the clinical sector, optimal conditions for state-of-the-art translational medicine and personalized therapy are being created. Early clinical trials (first-in-man und proof-of-concept in man) are performed in the Group's own facilities that meet GCP standards. The pre-clinical research units in the Fraunhofer Group for Life Sciences, working in compliance with GLP guidelines, contribute with their innovative research approaches to substantial reduction of the cost and time required for developing novel diagnostics and medications. For some indication areas, the Fraunhofer Group for Life Sciences has the expertise to cover the whole process from the molecule up to the patient, regarding both research and registration. Fascinating solutions for the highly specialized equipment that is required are at the Group's disposal: in fully equipped microarray facilities, the Group generates chips, for example for the analysis, recording, and comparison of gene expression profiles. The nONCOchip, which was developed as part of the research on non-coding RNAs (ncRNA), includes several tumor-relevant signaling pathways and is suitable for investigating a broad range of different tumor diseases.

Our experience in biohybrid test systems, in specific sensors for optical and acoustic imaging systems, in drug delivery systems based on nanoparticles, right through to prototype development for nebulizing systems is available to our clients. In compliance with Good Manufacturing Practice, the Fraunhofer Group for Life Sciences manufactures clinical investigational drug products – tissue engineering products, biologicals, and cellular therapeutics. Furthermore, the Group is well equipped for drug testing (pre-clinical and clinical). Complete phase-I and phase-II clinical trials, with a focus on respiratory diseases, are among the services we offer.

Many drugs and their metabolites are insufficiently degraded in even state-of-the-art sewage treatment plants. To prevent negative effects in downstream ecosystems, the Fraunhofer Group for Life Sciences offers services designed to meet real-life requirements: detection methods, bioaccumulation studies, and models for exposure assessment. The Group has developed a removal method based on nanostructured plastics for specifically removing pharmaceuticals from hospital wastewater. The ecologically compatible product design is particularly efficient and trendsetting. By making use of the Group's consulting services at an early stage of the development work, clients can save substantial costs and may actually prevent environmental problems from occurring.



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TOP-LEVEL: DIAGNOSTICS FOR INDIVIDUALIZED TREATMENT

Pharmacogenomics and pharmacogenetics

Chip-based technologies allow genome-wide gene expression profiles to be obtained. Based on the validated functions of these genes and their gene products, deductions can then be made about molecular changes in the organs, tissues, or cells under investigation. Completely equipped microarray facilities are available for this, so that biochips for this purpose can be developed in-house.

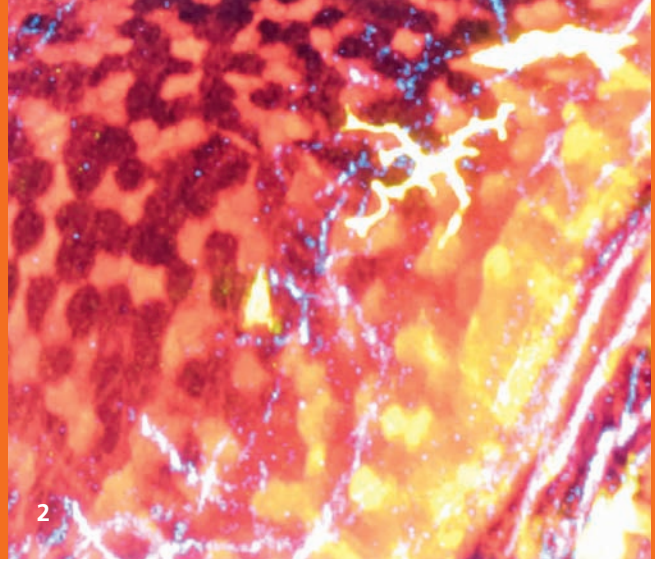
Using comparative gene expression profiles, the Fraunhofer Group for Life Sciences develops biomarkers that allow early assessment of pathogenesis, of the success of the intervention, and of unwanted side effects. Whether or not research should be continued can thus be decided at an early stage of drug development. The efficiency of clinical registration studies can be substantially enhanced by accurate and systematic stratification, as offered by the Group: as a result of different individual genetic situations, a drug product may induce unwanted side effects with different degrees of severity. Targeted screening measures allow those subjects to be excluded from the study in whom unwanted side effects are likely to occur. Both the number of clinical studies and the number of study participants can thus be reduced.

Whenever there are individual cases of serious side effects during non-stratified clinical studies, the scientists of the Fraunhofer Group for Life Sciences can even perform genomic analyses retrospectively using stored samples. Through comprehensive gene and protein analyses, they elucidate the mechanisms of action leading to these side effects. The insight gained from these analyses serves as a basis for ever more individualized treatment.

Recent studies have shown that in mammalian cells the transcriptomes – i.e. the total RNA transcripts in cells of a particular type or condition – are very complex. Particularly surprising was the result that at least 90% of the human genome is transcribed to RNA. Most of these RNAs do not include any signals for translation into proteins and are therefore referred to as non-coding RNA (ncRNA). This ncRNA represents an important cell-biological control level in complex organisms, which thus maps the condition of a cell or tissue very precisely. ncRNAs play an important role in particular in regulatory processes such as cell cycle control, cell differentiation, and cell death. It is, therefore, hardly surprising that a considerable number of different disease-associated and in particular tumor-associated ncRNAs have already been identified. Besides their role in cancerous diseases, ncRNAs seem to influence processes related to cell aging and immortalization.

Just like RNAs and transcribed proteins, ncRNAs represent important groups of potential diagnostic markers, which might enable the identification of subtypes of diseases and thus may provide important clues for personalized treatment. In addition, these molecules might also be potential drug targets. The Fraunhofer Group for Life Sciences is undertaking investigations in this direction, using methods of biomedicine and bioinformatics. The aim is to establish innovative platform strategies for the development of therapeutic targets and biomarkers and to translate these into clinical applications.

1, 2 *Observation of live cells*



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In vitro diagnostic systems

On behalf of its clients, the Fraunhofer Group for Life Sciences develops both complete *in vitro* diagnostic (IVD) systems and specific assay units for the constituent steps of the drug development process by using biochips. A proprietary scanner platform is available for this. For specific applications, a user-friendly evaluation program is provided and interfaces to bioinformatics tools are integrated.

Chip systems developed by the Fraunhofer Group for Life Sciences include:

– **nONCOchip:** The nONCOchip is a tailored microarray for screening ncRNA patterns. To support the search for novel biomarkers in tumor biology the nONCOchip has been equipped with 243,000 sensors. Of these, 60,000 are newly identified transcripts of ncRNAs which have been identified as relevant in transcriptome-wide studies on ncRNA expression in a large variety of oncological systems. Other customer-specific developments, for example for inflammatory diseases, are possible.
– **Deoxyribonucleic acid (DNA) chips:** The Fraunhofer Group for Life Sciences owns a pilot plant for manufacturing low-/medium-density DNA chips suited for small and medium series of up to 10,000 arrays per day. The arrays can also be captured in microtiter plate (MTP) format or directly in MTPs.
– **Protein chips:** Our specialists develop protein chips and provide both the antibody-based content and bioactive surfaces. Nano- and micro-chips are fabricated using different techniques, for example by coating surfaces with nanoparticles. Chemical methods and nanobiotechnological processes are used to adjust these chips to specific protein and peptide systems.
– **Cell chips:** The techniques developed by the Fraunhofer Group for Life Sciences allow, for example, for non-contact and parallel manipulation of suspended cells, which can simultaneously be characterized using image analysis.
– **Lab-on-a-chip:** For biochemical and molecular biological analytics, the Fraunhofer Group for Life Sciences has developed microfluid constituent systems for diagnostic biochips. Examples are an integrated silicon-based multiparameter biosensorchip and a hormone-based microarray chip for whole-blood diagnosis.
– **Automated *in vitro* cell culturing techniques:** The technologies developed in the European Commission's Integrated Project CellPROM for automated *in vitro* handling of individual cells under physiological conditions have made available a technology platform which allows cell culture automation for adherent cells to be implemented flexibly and according to user specifications.

Biohybrid systems

Biohybrid systems combine microtechnological components with biological systems in such a way that these can be used as novel bioanalytical or physiological sensors.

The characteristic feature of biohybrid systems is a miniaturization of technical functional units with integrated biological components. Biohybrid functional units are important components for novel concepts for the automation of analytical and diagnostic procedures.

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Biohybrid systems are being increasingly used in medicine and in biomedical research: on the one hand for collecting analytical data in medical diagnostic processes, and on the other hand as components of test systems for screening drug candidates and for evaluating different therapeutic options. In the Fraunhofer Group for Life Sciences, an interdisciplinary team of molecular and cell biologists, pharmacists, biophysicists, and engineers are working together as research and development partners at this interface between biotechnology, microsystem technology, and sensor technology. They are tackling a variety of issues relating to the development of cell- and tissue-based biosensor systems, drug delivery systems, implants, transplants, and gene therapies. The focus of their work concerns cardiology/angiology, neurology, oncology, and osteology. Examples of their development work are *in vitro* testing platforms for cardiovascular research and neurotoxicology, each combining the relevant cell models, and systems for non-destructive characterization of therapeutically relevant cellular material.

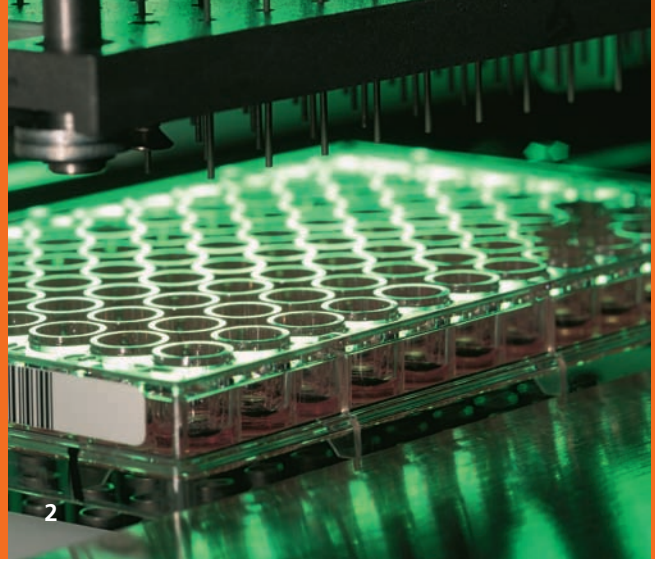
In vivo diagnosis using imaging techniques

The Fraunhofer Group for Life Sciences develops specific contrast media for molecular imaging, binding disease-specific antibodies to nanoparticles. In conjunction with appropriate imaging techniques, this enables earlier and more targeted diagnosis of in particular oncological disorders. The Group also designs specific coils for magnetic resonance tomography, in particular for micro-imaging up to a resolution of 6 µm. In addition, we utilize ultrasound sensors *in vivo* as non-invasive sensors and, based on these, develop acoustic imaging systems.

Non-invasive diagnosis

Analysis of the exhaled breath of patients with respiratory diseases provides important information on the type and severity of the disease. This allows, for example, inflammation mediators to be detected and their regulation determined. The Fraunhofer Group for Life Sciences offers such analyses as a service to external clients; measurement systems are available for measuring gaseous mediators (e.g. nitrogen monoxide) as well as non-volatile substances in the breath condensate.

1 *Analysis of the exhaled breath of patients as a non-invasive diagnostic tool*
2 *Biomedical screening platform*



RESEARCH FOR THE EARLY PHASES OF DRUG DEVELOPMENT

Target identification

Antibody-based technologies in combination with 2-D gel electrophoresis and mass spectrometry are used in the Fraunhofer Group for Life Sciences to detect and identify novel biomarkers of tumorous lesions. The scientists perform DNA sequence analyses and compare the gene expression profiles of healthy and diseased tissues, leading to the identification of disease-associated candidate genes and their tumor-specific proteins.

The "metabolome" is the complete set of metabolic products in an organism at a defined point in time. It enables a clear statement to be made about the organism's physiological condition as a function of a variety of parameters. Comprehensive analysis of the metabolome – referred to as metabolomics – is therefore of great importance in the diagnosis and classification of diseases and in the development of a prognosis; furthermore, it allows the impact of a pharmacological intervention to be determined.

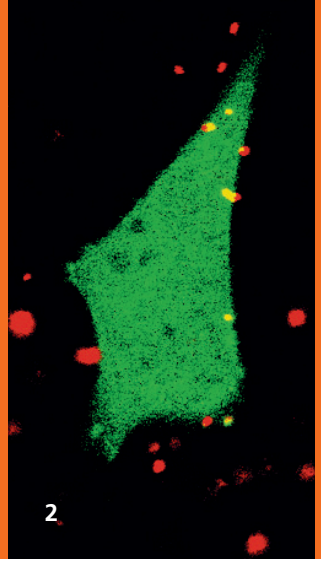
For the identification of new diagnostic and therapeutic target structures (target finding) and the development of novel therapeutic concepts, the Fraunhofer Group for Life Sciences possesses state-of-the-art methods of metabolomics, as well as molecular biological methods in the area of genomics and proteomics. Our aim is to provide and further develop leading-edge analytical methods.

New active substances (biopharmaceuticals)

The Fraunhofer Group for Life Sciences investigates and validates antibody-based active substances for use in oncological indications, allergies, and inflammatory and autoimmune diseases, as well as in infections (*Candida albicans*). Recombinant technologies are used for this, in particular to obtain antibody, enzyme, and cytokine fusions. For pre-clinical evaluation of these new drug candidates, the Group has access to all relevant *in vitro* methods, 3-dimensional organoid test systems, and a variety of different animal models.

Highly promising approaches for the development of novel medications are also being pursued in the field of pharmaceutical entomology; the focus here is on the development of new antibiotics that will also be effective against pathogens which are resistant to today's commonly used antibiotics.
A new protein has been detected in the larvae of the greater wax moth which interferes with the metabolism of bacteria. This protein inhibits metalloproteases of pathogenic bacteria of the genera *Clostridium*, *Pseudomonas*, and *Vibrio*. The structure and function of this protein were previously unknown and now offer promise for the development of novel antibiotics.

The search for novel oncological agents is also being pursued in pharmaceutical entomology; in this context, the insect realm is a promising resource for the detection of new lead structures. Not only the insects themselves, but also the microorganisms associated with them represent valuable resources for novel substances and are included in the research undertaken in the Fraunhofer Group for Life Sciences.



1 *Biodegradable nanoparticles as drug delivery systems*
2 *Functionalized nanoparticles (red) docking to a target cell (green)*
3, 4 *GMP manufacture of investigational drug products in state-of-the-art clean-room facilities*

Rational protein design

The Fraunhofer Group for Life Sciences has at its disposal the complete infrastructure for protein synthesis and structure analysis. Besides crystal growing, this also includes diffraction analysis and the computer hardware required for structure analysis. In the search for protein-based active substances, *in silico* screening methods are becoming more and more attractive. Structural data in combination with microcalorimetric results are used in this context for rational protein design.

Nano-/microparticle-based drug delivery systems

Another focus of research is nanoparticle/nanobead and microparticle systems and their biofunctionalization. The particles consist of organic polymers, sol-gel-generated hybrid materials, or inorganic materials. Molecular imprinting, chemical surface functionalization, and immobilization of biomolecules are the technologies the Fraunhofer scientists use to biomimetically modify the surfaces of nanoparticle systems. In addition, they develop biodegradable long-term depots.

3D test systems

Three-dimensional organoid test systems exhibit organ-specific functions and are thus particularly well suited for cellular and molecular biological analyses of pharmaceutical, cosmetic, and chemical ingredients. These systems, produced on the basis of human organ cells and certified according to DIN ISO 10993-5, can replace animal experiments. The Fraunhofer Group for Life Sciences further develops such test systems and establishes, for example, vascularized organoid structures which have both an intact capillary system and afferent artery and an efferent vein. This not only allows the development of defined tissue and organ structures; it also opens up for the first time the possibility of culturing human vascularized tumors *ex vivo* and subjecting them to treatment for a period of up to three weeks. The effects of the treatment can be demonstrated macroscopically, histologically, and molecularly at the cellular level. The results can be analyzed chronologically as well as in relation to the individual patient.

Pre-clinical test models

A high percentage of drug candidates fail even as late as in clinical phase-I and -IIa trials due to insufficient kinetics, lack of efficacy, or unexpected side effects. Models allowing for reliable predictions in these areas during pre-clinical research and development are, therefore, urgently required. The Fraunhofer Group for Life Sciences develops approaches for pre-clinical trials with human cells, tissues, and stem cells, placing the emphasis on system biology approaches.

Aerosol technology for administration by inhalation

The Fraunhofer Group for Life Sciences develops nebulizing systems for liquid and solid pharmaceuticals and creates prototypes. Positive results have been obtained also with substances such as proteins, peptides, and DNA/RNA vectors, which represent a great challenge as they are sensitive to mechanical forces and easily change their conformation during aerosolization. Furthermore, we characterize nebulizing systems using spray visualization by particle image velocimetry (PIV) or by means of particle size distribution analyses.

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THE WAY INTO THE CLINIC: CLINICAL INVESTIGATIONAL DRUGS AND REGISTRATION TRIALS

Active biopharmaceutical ingredients for pre-clinical and clinical trials

The Fraunhofer Group for Life Sciences develops manufacturing processes for biopharmaceutical candidate drugs and manufactures pilot batches for early-phase clinical trials in compliance with the Good Manufacturing Practice (GMP) guidelines. Heterologous expression systems based on microorganisms (*E. coli*), plants, and mammalian cells (CHO) are normally used for this. This allows antibodies, growth factors, ligands, and nucleic acids to be provided as raw materials for clinical investigational drug products. But also specialties such as bacteriophages, viruses, and virus-like particles can be manufactured on a gram scale for clinical trials.

A category of increasing importance is that of active ingredients based on antibodies and nucleic acids. They are duly considered by the Fraunhofer Group for Life Sciences in fundamental research to develop platform technologies comprising robust and standardized production cell lines, culturing techniques, and strategies for purification of the active ingredients. The aim is to use platform technologies for the manufacture of investigational drug products and to optimally exploit the synergy within the Fraunhofer Group for Life Sciences in order to significantly reduce the time span from the idea stage to clinical testing.

For the manufacture of active pharmaceutical ingredients for pre-clinical and clinical research, multi-purpose GMP facilities with bioreactors for cell culturing and appropriate process chromatography and filtration systems are available. These facilities comply with the requirements of both the European Medicines Agency EMEA and the American Food and Drug Administration FDA. In addition, the Group operates a GMP clean-room unit for the aseptic filling and finishing of clinical investigational drug products.

Pre-clinical studies

For drug testing, animal experiments continue to be mandatory in many areas. The Fraunhofer Group for Life Sciences offers investigations and toxicity studies in rodents and non-rodents, performed in compliance with GLP regulations, in order to analyze, for instance, aspects of toxico- and pharmacokinetics. These studies allow subchronic and chronic toxicity to be recognized, and furthermore carcinogenic, teratogenic, and mutagenic effects can be identified. Different models are available for the study of respiratory diseases such as allergies, inflammations, infections, asthma, and chronic obstructive pulmonary disease (COPD).

In vitro methods are used whenever possible to replace animal experiments. Of special importance in this regard are studies in primary human cells as well as in whole pieces of tissue using the precision-cut slice technology.

1 *Well-trained staff competently attend to the participants of clinical trials*

Phase-0 trials

The institutes of the Fraunhofer Group for Life Sciences are capable of conducting both pre-clinical and clinical trials for respiratory diseases in-house. Important aims of the Group include the definition and introduction of a phase 0 in clinical testing, featuring administration of the drug candidate to humans at a very early stage and at very low doses. This low dosage, corresponding to one hundredth of the pharmacologically effective dose, requires sufficiently sensitive analytical methods: high-performance liquid chromatography combined with tandem mass spectrometry (HPLC-MS/MS). This guarantees seamless integration of pre-clinical investigations and clinical trials.

Clinical trials airways

The Fraunhofer Group for Life Sciences conducts phase-I and -II clinical trials for the registration of pharmaceuticals, the focus being on diseases of the respiratory tract with the indications asthma, COPD, and allergic rhinitis. Due to the challenge chambers for airborne allergens (grass pollen, house dust) which the Group has at its disposal, there is no necessity to perform field studies. Superior clinical research expertise exists in the field of segmental allergen challenge and segmental drug administration with a bronchoscope as well as in the collection of lung lavage fluid and biopsies for a wide range of endpoints including gene and protein expressions. The studies are performed in compliance with GCP requirements.

Translational research

In spite of enormous investment in research and development (R&D) on the part of the pharmaceutical industry, the relative return on that expenditure as determined by the number of registered novel medications is continually decreasing. Ninety percent of all drug candidates fail because of deficiencies in efficacy and/or safety after the first trials in man. This shows that there is a major problem transferring pre-clinical studies to the clinical situation. The aims of translational research are to assure better “translatability” of early development data to late clinical data and thus to increase the reliability of predictions. In close cooperation between research organizations and clinical institutions, new methods are jointly developed which directly implement the results of basic research in disease prevention, diagnosis, and therapy. Vice versa, observations made in patients can quickly be communicated to the scientists involved in basic research.

By means of a methodological, systematic translation process, the aim is to develop methods and processes that offer high predictive reliability and are therefore capable of supporting the critical step from the pre-clinical to the clinical stage. This includes the establishment of new validated biomarkers, phase-O clinical trials with micro-doses of the candidate drug, and also high-throughput methods of modern molecular biology to enable integration of comparisons between patients and healthy volunteers.

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2 *Microcosm growth*

PHARMACO-ECOLOGY – ENVIRONMENTAL RISKS AND SIDE EFFECTS

Pharmaceutically active substances may be introduced into the environment in a variety of different ways. The main source is humankind, excreting previously ingested medicines or disposing of remainders via the sewage system. Many pharmaceuticals are soluble in lipids (lipophilic) and thus likely to accumulate in the environment (bioaccumulation). Therapeutic preparations are designed to be stable and may therefore persist in the environment for a long time, in particular when they are deposited in sediments. Problems are caused above all by substance mixtures, which induce specific effects that are desired in the human patient but may lead to unwanted effects in the environment, even at low concentrations and over a long period of time.

Assessment of potential environmental risks of pharmaceuticals

Many studies have provided evidence of the presence of pharmaceutical agents in bodies of water and sediments. This is why the registration of new drugs requires an ever increasing amount of testing with regard to their environmental behavior. The Fraunhofer Group for Life Sciences has many years of experience in environmental chemistry and ecotoxicology and performs such testing on behalf of its clients. In the assessment of risks both to consumers and to the environment associated with pharmaceuticals and their residues, the Group pursues an integrative strategy. This strategy includes sensitive detection methods, ecotoxicity tests and bioaccumulation studies, models for exposure assessment, and biotechnological and procedural elimination processes.

Ecologically compatible product design

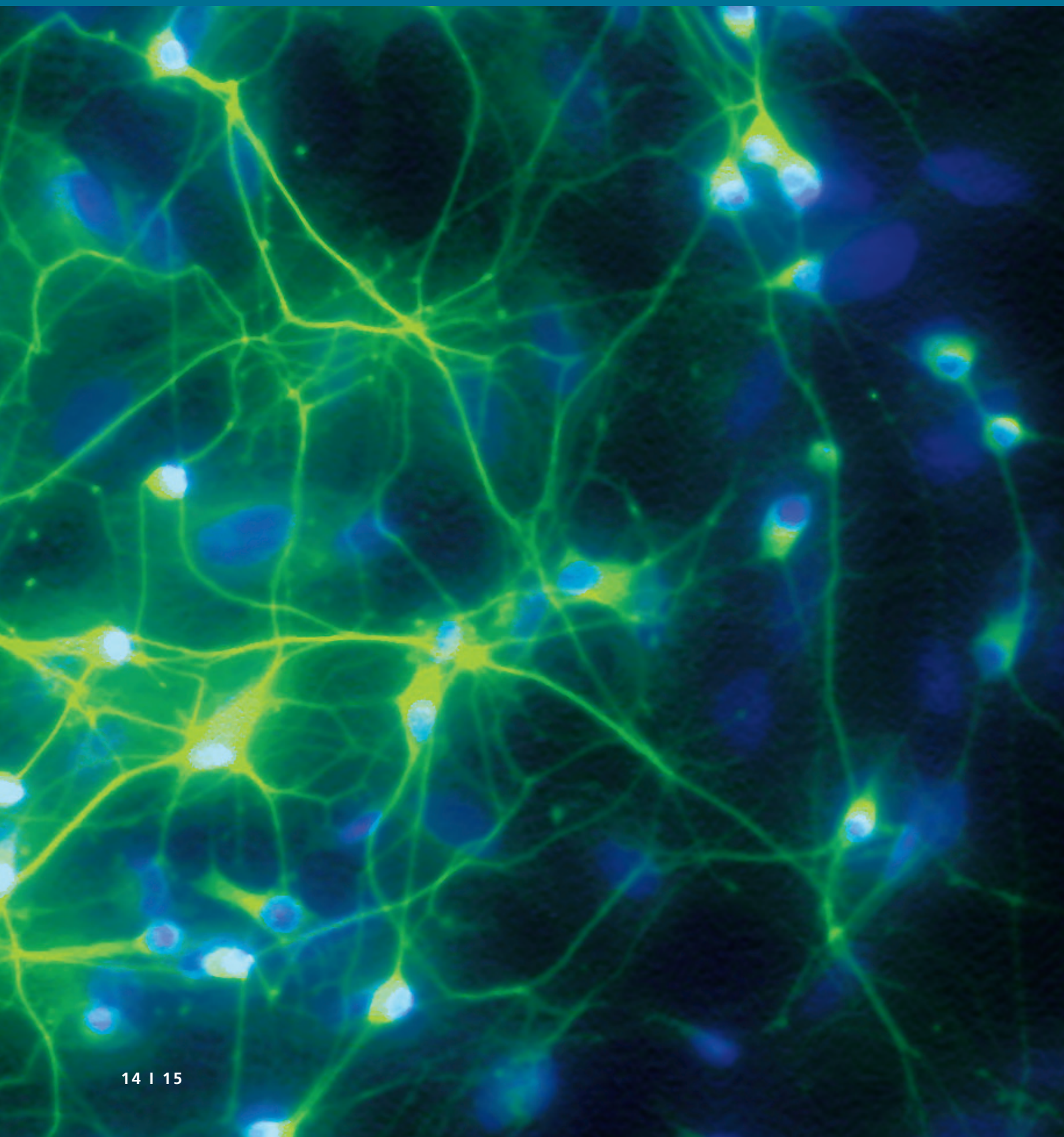
Fraunhofer scientists collaborate in ecotoxicology and toxicology committees and are thus involved in the elaboration of fundamentals that serve as a basis for draft submissions to authorities and for the definition of requirements to be met by future pharmaceuticals. For the pharmaceutical industry, we conduct studies and develop models for ecologically compatible product design. Expert reports created at an early stage in the drug development process put companies in a position to save unnecessary expenses.

Specific removal of pharmaceuticals from the water cycle

As the available methods for degradation and removal of pharmaceuticals from wastewater, such as ozonolysis or adsorption on activated carbon, are either very costly or the process itself may produce toxic degradation products, we are 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 – a process referred to as "molecular imprinting". It creates selective molecular recognition sites in the polymers (NanoMIPs), which remain after the manufacturing process.

In a model, we were able to adsorb 500 micrograms of pentoxifylline, which is a widespread micropollutant, in one gram of the NanoMIPs. Pentoxifylline has been classified in the highest water pollution class – namely it is considered to be "severely hazardous to water". The specific adsorber beads can be incorporated into a membrane. It is also possible to give the beads a magnetizable core to allow for 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) NanoMIPs may help minimize pollution or even prevent such pollutants from being introduced into the water cycle via contaminated wastewater.

REGENERATIVE MEDICINE: THE CHALLENGE OF QUALIFIED BIOBANKING AND CONTROLLED SELF-HEALING



OVERVIEW

All phases of tissue growth have a particular meaning for the body's own self-healing powers. Researchers in the Fraunhofer Group for Life Sciences have managed to influence all these phases – from the stem cell and its differentiation to a specific cell structure, to tissue and through to the implant – by systematic stimulation and control mechanisms. For each stage of this process, the Group can utilize research and development results on novel therapeutic approaches, its own methods, and its specialist know-how. Particularly good results have been obtained with adult glandular stem cells. After targeted differentiation, these are currently being tested in cardiac infarction and skin replacement models. Complex cell-therapeutic concepts have proven beneficial, for example, to control immunological processes and to treat tissue damage after stroke.

To support healing processes or as a replacement in case of extensive tissue loss, the Fraunhofer Group for Life Sciences can grow biological tissue, in particular cartilage and skin, in its own GMP laboratories where all necessary regulatory expertise is available. Up to now, this has been a manual process for the most part, but the development of novel, fully automated tissue engineering plants is already well advanced.

Biomarkers play a key role in the life sciences. They can be successfully identified and validated by comparing as many samples and case cohorts as possible. A prototype of networked biobanking is the CRIP bio-database (Central Research Infrastructure for molecular Pathology), which is used to store data obtained by standardized sampling and sample asservation procedures. Actual samples are stored and preserved for future use in EUROCRYO, the European research database maintained by the Fraunhofer-Gesellschaft. The Group thus has at its disposal a biobank which is unrivaled worldwide regarding its system and content.

1 *State-of-the-art cryotechnology*

THE CELL IS THE BASIS

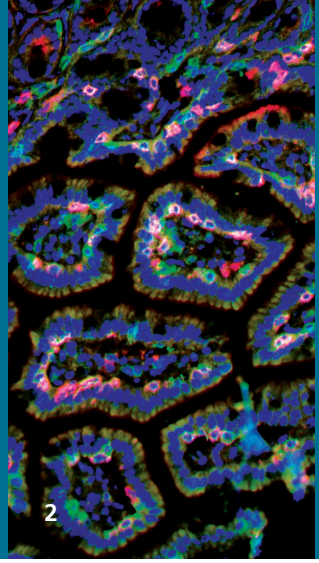
Regenerative medicine aims to copy the healing and repair processes which continually take place in the human body. These natural healing and defense mechanisms may perform differently in every individual body. If a body has reached the limits of its own natural capabilities for dealing with a particular lesion, further healing processes can be stimulated or mimicked with the means provided by regenerative medicine. Biological replacement cells or tissues are used and the body's own repair processes are stimulated so as to restore tissue or organ functions.

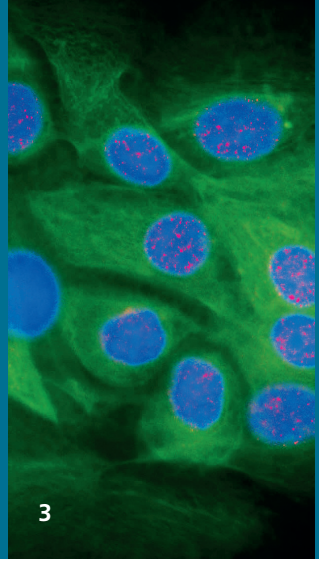
The core expertise of the Fraunhofer Group for Life Sciences includes work with stem cells, and in particular adult stem cells. The extensive experience of the Group with these systems forms the basis for the development of novel handling systems and devices for the transfer, differentiation, and dedifferentiation as well as for the cloning of single cells.

Qualified biobanking

The Fraunhofer Group for Life Sciences has worldwide unique expertise in the technology and processes of cryoconservation of cells and small tissue segments. Cells may thus be stored without loss of quality and subsequently used for research, biotechnological applications, or therapeutic purposes. In the European research cryobank of the Fraunhofer-Gesellschaft, EUROCRYO, valuable and unique collections of cells (live samples) are stored in a way designed to meet the requirements of modern biotechnology. Retrospective investigation of samples, therefore, provides relevant information even after decades. Core elements of the underlying concept are miniaturization and highly parallel sample storage. Thanks to novel storage substrates, the microsystem-based cryotechnology developed for this purpose allows the number of possible cryosamples to be increased by a factor of 100 during the first miniaturization step. To rule out any risk of sample confusion, an electronic storage unit with a capacity of up to 1 GB and which is readable and writable even at temperatures around -180 °C, is kept together with the samples. The methods developed are characterized by high vitality rates and are thus particularly well suited to stem cell research and preservation. The services offered by the Group based on this expertise include the design, construction monitoring, and setting up of cryobanks and cryo-specific equipment for medical, biology, and drug research applications right up to industrial scaling.

2 *Detection of intraepithelial intestinal lymphocytes*
3 *Keratinocytes*





New strategies for targeted stem cell differentiation

Recent findings in stem cell research have provided evidence that a very efficient method for making stem cells differentiate into a particular cell type is the coculturing of stem cells with other cells or tissue biopsies. The hypothesis is that important external signals controlling the identity of a cell are given locally by the target tissue; which means, for example, that an adult stem cell penetrating into an injured heart will receive the decisive signals to differentiate into a heart cell from the heart tissue itself.

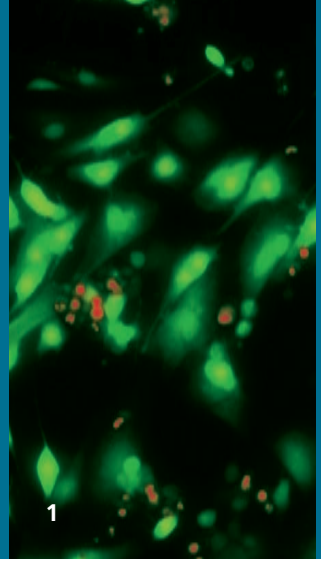
In this research area, the Fraunhofer Group for Life Sciences benefits from the results and experience gained during many years of stem cell research. Glandular stem cells are cocultured in direct or indirect contact with tissue biopsies – depending on the type of cell and tissue. In the case of direct coculture, tissue biopsies are added to adherently growing cells in the culture containers. For indirect coculture, tissue biopsies and stem cells are placed in separate coculturing containers to enable spatial separation. This system allows an exchange of messenger substances and signals, however, at the same time it prevents the biopsy cells from getting through to the stem cells. This method has up until now been successfully used to induce an accumulation of nerve cells via brain biopsies and an accumulation of cardiomyocytes via heart biopsies. First results of these investigations are already being implemented in the development of strategies for heart tissue regeneration. To this end, stem cells are cultured on biodegradable meshes and induced to differentiate into cells similar to cardiomyocytes. These meshes are currently being tested in a model of myocardial infarction.

Reprogramming of cells

Not only stem cells, but all therapeutically relevant cell populations in general bear the hope of enabling successful treatment of diseases which so far have been considered untreatable. This holds true in particular for diseases involving a loss of cells and thus of functionality. The possibilities for therapeutic use, however, go far beyond the actual replacement of cells. Benefits have also been demonstrated for the prevention or mitigation of degenerative processes.

A major challenge for biomedicine in this context is to make adult stem cells available in sufficient quality and quantity for therapeutic purposes. The Fraunhofer scientists have developed a method for producing patient-specific, individualized stem cell lines from somatic cells without viral integration or genetic modification (induced pluripotent stem cells – iPS). These iPS cells display the typical characteristics of embryonic stem cells without, however, engendering ethical controversy.

A special focus in this research work is the generation of iPS without the use of viruses. Different types of reprogramming, including those with specially developed media compositions, can be explored, for example fusion, nuclear transfer, and stem cell extracts.



1

Immunodiagnostics and cellular diagnostics

For the demonstration of cells and cell functions in tissues and the prediction of therapeutic responsiveness, the Fraunhofer Group for Life Sciences offers a variety of analytical and diagnostic techniques: cell-imaging diagnostics and follow-up, cell function analysis, innovative tissue typing, and pharmacogenomic investigations on inflammatory processes. Using the cells and tissue cultures developed in the Group, the Fraunhofer scientists can investigate the functionality of diagnostic and therapeutic concepts in complex systems close to the real-life situation.

Immunomodulation and cell therapy

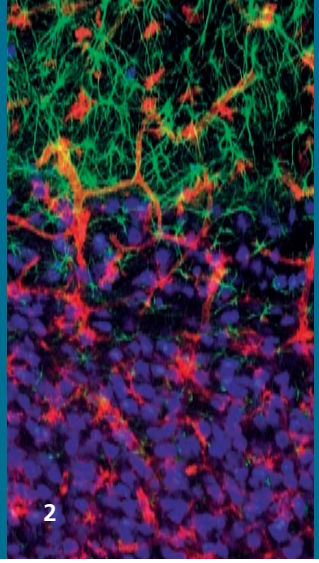
The scientists of the Fraunhofer Group for Life Sciences develop strategies for immunological tolerance induction, tolerance monitoring, and controlling the functions of the immunological system. These enable successful immunological management of tissue rejection reactions. Through cell isolation and preparation, cell apheresis, and cell proliferation *in vitro*, the Group further develops therapeutic concepts. To this end, the scientists of the Group use cell suspensions, mainly with progenitor and stem cells. A focus of research in this area is on new cell-therapeutic approaches to treat tissue damage resulting from stroke. With its possibilities for low-temperature conservation and a standardized and patented isolation method the Fraunhofer Group for Life Sciences has at its disposal a variety of stem cell cultures which are available nowhere else in the world. These are cultures of different tissues from widely differing animal sources right through to human stem cell cultures, with excellent growth rates, good differentiation possibilities, and suitable for long-term culturing.

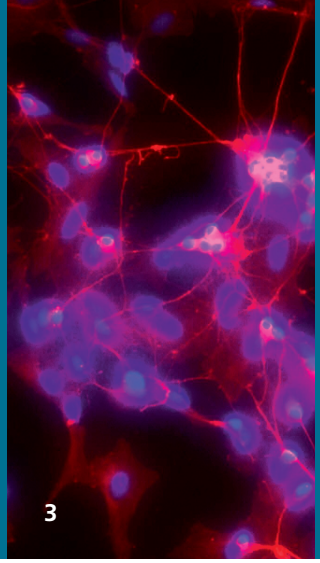
Manufacture of cellular therapeutic agents

The clinical testing of medications for novel therapies requires top-quality clinical investigational drug products, which must be manufactured in compliance with GMP regulations. The Fraunhofer Group for Life Sciences not only has clean-room facilities for the production of biopharmaceuticals, but also clean-room facilities specially designed for the manufacture of cellular and tissue preparations and complying with the most recent technical and regulatory standards. A special feature of these facilities is the subdivision into separately accessible clean-room suites, meaning that individual cellular products for each client can be continuously provided. A consistently high quality level is ensured by an excellently equipped quality laboratory, highly qualified staff, and a comprehensive quality management system.

The treatment of oncological diseases with cellular therapeutic agents is one of the most recent treatment strategies, which is currently being tested worldwide in clinical studies. The Fraunhofer Group for Life Sciences has the capability to produce and optimize both cytokine-induced killer cells and dendritic cells specifically for each patient. All steps from process development through to acquiring the manufacturing license are accomplished by the same organization.

An advanced stage has been reached in the development and practical implementation of a GMP manufacturing process for an autologous cellular therapy for ischemic stroke.





1, 2, 3 *Research on stroke*

Risk analysis for regenerative strategies

The development of novel regenerative strategies requires the biocompatibility of the products to be tested as comprehensively as possible in murine and human systems. This assures speedy development of the products up to their preclinical and clinical application. In the Fraunhofer Group for Life Sciences, risk profiles of products are being generated by using *in vitro* and *in vivo* analyses. They take into account, for example, immunological tolerability, cytotoxic, proliferative, and stimulating effects on primary, stem, or tumor cells, as well as thrombogenic, hemolytic, or genotoxic activity. A large variety of specialized mouse models are employed for complementing *in vivo* experiments.

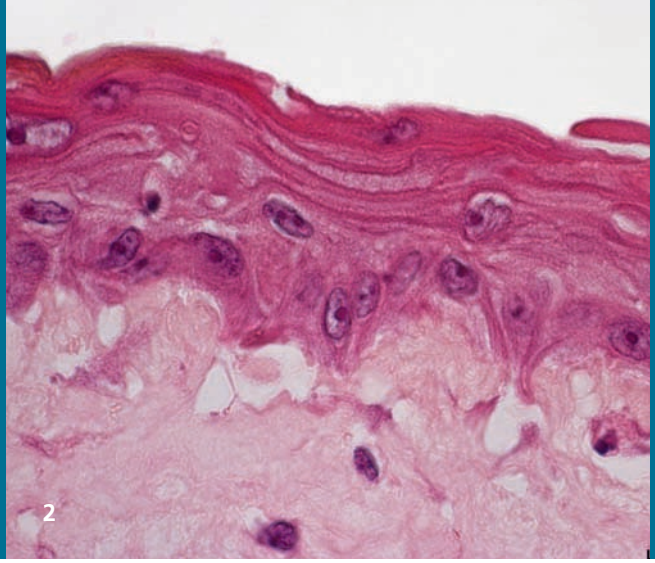
In addition, the Group collaborates with a competent partner who has an accredited diagnostic laboratory in order to carry out clinical studies.

The bio-database CRIP – "Central Research Infrastructure for molecular Pathology"

"Bio-bases" are collections of biological materials and corresponding data.

An infrastructure across different biobases and institutions – also referred to as "bio-database" – is gaining more and more importance in biomedical research and development for tasks such as the identification and validation of biomarkers. The "Central Research Infrastructure for molecular Pathology" CRIP is such a bio-database, which has been operated inside the Fraunhofer Group for Life Sciences since 2007 and is being further developed as a prototype for other research areas. The rights of the partner bio-bases regarding the respective data and samples stored in the bio-database continue to be safeguarded, as are the personal rights of the sample donors and the data privacy regulations. Studies on multifactorial diseases and individualized treatments require ever increasing numbers of samples and case cohorts, which a single clinic would not be able to collect or only over a very long time span. This is why medical bio-bases in particular have to also be networked to each other by means of bio-databases. Prerequisites for this include standardized sampling and sample asservation procedures as well as a data network which fulfills the relevant ethical and legal standards.

Human tissue samples are of particular relevance for research as they enable investigation of both locally restricted diseases (such as cancer or inflammation) and organ-specific manifestations of systemic conditions. In contrast to other body substances such as blood or serum, tissue samples are not reproducible. The consolidation of tissue banks in bio-databases – for example in the "Central Research Infrastructure for molecular Pathology" (CRIP) – therefore aims to overcome a bottleneck in research.



1 *Three-dimensional skin test systems*
2 *Tissue slice from a skin substitute*

TISSUE ENGINEERING

The term tissue engineering refers to the reproduction of natural tissue from primary cells under laboratory conditions. This tissue can be used to support healing processes, to regenerate tissue that has become dysfunctional, and to replace destroyed tissue such as burnt skin. The procedure to manufacture a ready-for-use tissue engineering product involves two main phases. The first phase consists of establishing and verifying a procedure that leads to the desired product; the second phase consists of adapting this procedure to the medical regulatory requirements. This process is subject to a high degree of formalization and authorized documentation. The Fraunhofer Group for Life Sciences as a competent research partner in medicine and medical technology develops tissue engineering processes and products, including appropriate carrier structures; GMP laboratories for the manufacturing of autologous transplants are also available.

Another focus is the development of three-dimensional test systems with organ-specific properties; these are suitable for *in vitro* testing of substances in medical engineering, cosmetics, and the pharmaceutical and chemical industries.

Manufacturing technology for tissue engineering

Tissue engineering has been a focus of research for several years already, and many biotechnological laboratories are producing tissues such as cartilage or skin. So far, however, the cultivation of transplants such as skin grafts is a costly process, because most steps are performed manually. The provision of tissue structures at reasonable price and above all quickly continues to be one of the major challenges of tissue engineering. Only by complete revision of the production technology, processes, and methods via interdisciplinary collaboration of researchers from the life sciences and the engineering sciences will it be possible to unleash the enormous potential of tissue engineering in an integrated approach.

This challenge has been taken on by the scientists in the Fraunhofer Group for Life Sciences: together with colleagues from the Fraunhofer institutes for manufacturing engineering and automation technology they are working on a fully automated tissue production process. The machine-based process has been subdivided into individual modules, so that the requirements for the manufacture of different tissues can be met. Further development work is required before the final machine for "tissue engineering on demand" will be ready for the market. But it is already clear today that this will open up a variety of new possibilities in the medical area.

Automated tissue engineering is also an interesting option for chemical, cosmetics, pharmaceutical, and medical companies that require tolerability testing of their products.

3 *Three-dimensional intestinal test system*

3

New stem cell sources for tissue engineering

The treatment of acute and chronic skin lesions has long been a domain of secondary health care with sophisticated plastic-reconstructive interventions. Every year, thousands of burned individuals and hundreds of thousands of patients with chronic wounds of different origins require their wounds to be closed in order to prevent loss of fluid and electrolytes, infections, metabolic dysfunction, immunosuppression, pain, and amputation. The development and use of artificial skin substitutes that are capable of achieving the most relevant properties of human skin allow wounds to be closed immediately and support regeneration.

Biological skin substitutes are three-dimensional systems consisting, for example, of collagen fibers and elastin, enabling immediate wound closure and serving as a fiber scaffold for permanent regeneration of functional autologous dermis. A further optimization of artificial skin substitution methods might be able to be achieved by combination with stem cells differentiating into skin structures or releasing growth factors that would accelerate and/or improve the regeneration process. One focus of the Fraunhofer Group for Life Sciences in the area of cell differentiation is the characterization and utilization of adult stem cells from exocrine glandular tissue. Multi-potent stem cell populations with similar properties can be isolated from pancreas tissue, salivary glands, and skin. Studies in this area have already demonstrated that a skin substitute colonized with pancreatic stem cells leads to accelerated wound healing and improved vascularization of total skin defects in a murine animal model.

Biomaterials are opening up new possibilities

The interaction between the material and the relevant biological system is of pivotal importance for the success of tissue engineering. By combining expertise in materials science and experience in cell biology, the Fraunhofer Group for Life Sciences develops bioactive, biocompatible, or bioinert materials for use in medicine and medical engineering – one example of the possibilities of interdisciplinary cooperation within the Group. Using plasma technology, for example, implant materials can be prepared in such a way that proteins will not adsorb non-specifically; on the other hand, a coating with growth factors may be applied so as to promote the adhesion of mammalian cells. The biocompatibility of surfaces is of great importance also for artificial extracellular carrier structures. Only good biocompatibility will guarantee the proper functioning of the adjacent biological systems.

HEALTHY FOODS: THE CHALLENGE OF HIGH CONSUMER ACCEPTANCE AND DISEASE PREVENTION

OVERVIEW

A large variety of effects during transportation, processing, and packaging can impair the safety or quality of our foods. For all phases of the product life cycle – starting with tests on the animal feed, single components, and complex substance mixtures right through to proof of functionality required for health claims – the experts in the Fraunhofer Group for Life Sciences can provide you with competent advice.

The most important selling point for a food product, namely its taste, is at the same time a highly sensitive product feature. To analyze this feature the Group not only performs analytical tests in a sensory laboratory, but particular emphasis is also placed on evaluation by a well-trained sensory panel. The Group can thus detect and systematically influence the formation of off-odors from precursor substances and their dependence on production and process parameters; solutions developed by the Group in this context include the new high-frequency field method for pasteurization and sterilization as well as the customized design of packaging systems in the Group's competence center for "Active and Intelligent Packaging".

Foods that provide an additional physiological benefit allow consumers to place a focus according to their individual requirements, for example to prevent overweight and cardiovascular diseases. The Fraunhofer Group for Life Sciences develops processes for this purpose and adapts food formulations. Bioactive additives to satisfy the increasing health awareness of consumers entail completely new challenges. The Group's holistic approach is clearly visible in the example of omega-3 fatty acids: dramatically shrinking marine fish stocks and issues of product safety and odor prompted Fraunhofer scientists to explore alternative resources for fish oil capsules, which are very popular because of their high content of omega-3 fatty acids. A promising result was found to be eicosapentaenoic acid (EPA), which also belongs to the omega-3 fatty acids. An efficient manufacturing process based on the marine microalga *Phaeodactylum tricomutum* is now also available, and the Group's photobioreactors meet all criteria for an industrial EPA production. The proof of efficacy required for making health claims can finally be provided by the Group by means of validated *in vitro* tests which enable quick verification of the functionality in cell and tissue cultures, and by means of the standardized CaCo-2 test for absorption analyses. Even a three-dimensional vascularized intestinal model is available for absorption, toxicity, and metabolism studies.

1, 2 *Expertise on a wide range of foods*

FOOD SAFETY AT ALL STAGES OF THE PRODUCT LIFE CYCLE

Consumers in Europe today have access to the whole array of foods produced worldwide. Our multifaceted and complex diet is, however, also very susceptible to unwanted perturbation. Consumers take it for granted that their food is safe and of high quality – indeed safety must be ensured at all stages of the food production chain. This holds true for the production of the ingredients during crop growing or animal rearing and also for the processing and low-germ or aseptic filling and finishing of the food products right through to optimal packaging processes and materials. The Fraunhofer Group for Life Sciences offers solutions for all stages of the product life cycle in the food industry.

Industry today faces three major challenges in order to guarantee the safety of foods. In addition to microorganisms, it is in particular chemical contaminants and allergens which are of relevance for food safety. In order to avoid these risks, the Fraunhofer Group for Life Sciences optimizes processes and develops and applies suitable analytical monitoring methods for all stages of the food production process on behalf of its clients.

Ingredients

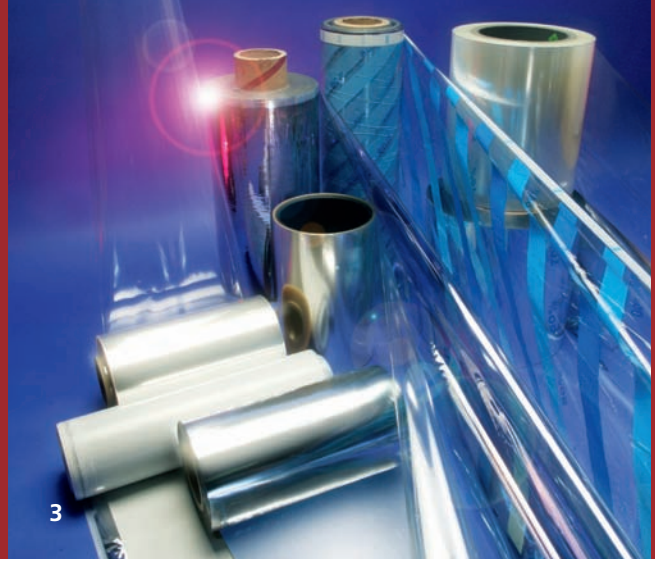
The key technologies of the 21st century – biological and genetic engineering – are increasingly used also in the food and animal feed industries. Users of these technologies who call on the services of the Fraunhofer Group for Life Sciences can safely assume that the most recent R&D findings in these areas are taken into consideration. New additives lead to modifications in the composition of our foodstuffs and animal feeds. Our specialists are prepared to conduct the necessary investigations on individual food and feed components, but also in complex substance samples.

Some substances generated *in situ* during the production process may affect product quality. They can be detected by ultra-trace analysis even in complex food matrices. The Fraunhofer scientists are thus creating the basis for optimizing existing processes in such a way that these contaminants are not generated at all or only in much lower quantities.

In addition to their technical know-how, the Fraunhofer scientists have many years of experience in the assessment of potential health hazards. Risk assessment and highly sensitive analytics complement each other to enable safe foods providing great pleasure to be offered to consumers.

Screening methods of molecular and cell biology

In addition to the traditional chemical analyses and toxicological investigations, the Fraunhofer Group for Life Sciences develops screening and express tests based on molecular biological procedures. These are developed individually to respond to specific problems in industry or for food quality monitoring – such as microbial contamination or the occurrence of allergens – and can thus be used in a customer-specific manner. By using high-throughput PCR and chip-based procedures, whole batches can be tested quickly and at low cost. In the future, effect-based cell assays will also play an important role in this context.



3 *Functionalized packaging films*

However, precautionary measures against undesired contaminants during the production process are not the only issue of decisive importance in the modern food industry. It is also vital that the species purity of the raw materials used can be guaranteed. The processing industries are increasingly demanding express tests for an initial analysis of raw materials. The Fraunhofer Group for Life Sciences is therefore intensively developing such test systems to enable low-cost and quick determination of the species purity of raw materials based on a lab-on-a-chip system.

Microbiological safety

Once packaged, only sufficiently stable foods can be stored for a prolonged period of time without losing their high quality and posing a risk to consumer safety. This is achieved by treating not only the actual food product, but also subjecting the packaging material to a decontamination process. Wet-chemistry processes are still mostly used for sterilization today. The validation of the efficacy of these sterilization processes in industrial use is one of the focuses of the Fraunhofer life sciences institutes. As a future alternative to wet-chemistry procedures, the use of gas plasmas is actively being explored. Decontamination and sterilization will thus soon be able to be performed non-thermally and, above all, without leaving any residues.

Currently very popular are convenience products – for example double-fresh meals, which are complete meals composed of different raw ingredients that are packaged together. For these highly sensitive convenience products, scientists have also found a special solution: antimicrobial substances which are integrated directly into the packaging material help preserve the high quality of the packaged foods.

There is furthermore a trend towards food products whose natural ingredients have been modified as little as possible. Food producers can only fulfill both these consumer wishes using very gentle preservation techniques – and this represents another challenge. Fraunhofer scientists have developed a novel high-frequency heating method for the gentle preservation of foods.

Interactions with packaging materials

Packaging materials and utensils which come into contact with foodstuffs have to be tested and assessed for their suitability. We develop the physico-chemical analytical methods required for this – in particular for trace and ultra-trace analyses and for permeation analyses. We have many years of experience studying interactions between packaging materials and the packaged goods, in particular regarding the migration of additives from polymers or paper into food products. Migration tests and migration modeling in this context are among the services we offer, in addition to the identification of off-odors or odor losses through the packaging. The Fraunhofer Group for Life Sciences has recently started undertaking research aimed at assessing consumer exposure to migrating substances.

The most important test procedures have been accredited according to DIN EN ISO/IEC 17025. The Fraunhofer Group for Life Sciences shares its experience and competence by participating in all relevant European and national committees for the standardization and assessment of food contact materials.

1, 2 *Consumer protection as a central issue in research*

QUALITY IN TUNE WITH PLEASURE

The continuous pasteurization or sterilization methods used today involve slow temperature adjustment processes and long treatment times. This considerable thermal stress often results in a substantial loss of flavor and important nutrients and often also modifies the color and texture of the food. Remarkable increases in quality can be achieved by heating up temperature-sensitive foods quickly and evenly. For fluid and pasty foods we have already been able to develop an effective procedure: by using electrical high-frequency fields, these foods can now be heated very quickly and gently.

Food design for optimal food texture

Food texture is an important factor contributing to the customer's sensory pleasure. Proteins and fibers play a decisive role here. The search for appropriate raw materials and the systematic modification of the vegetable proteins and fibers obtained from these are one focus of research in the Fraunhofer Group for Life Sciences. Different procedures – thermal, physical, or enzymatic – can be used for such modifications. Products such as baked goods and pasta or homogenized products such as salad creams, drinks, spreads, ice cream, and meat pastes each have their own specific texture. Using the methods developed by the Fraunhofer scientists, ingredients can be tailored to a wide range of different types of products.

Flavor

The specific flavor of a food product is the result of a complex interaction of many different factors. Numerous research and development activities in this area are therefore aimed at gaining a better understanding of the process-structure-property relationships. The relationship between flavor and texture, for example, has not yet been comprehensively elucidated, nor has the impact of processing and hygienization methods on the preservation of flavors.

Novel ingredients with special technological or health properties may also affect the taste of a food product. Fraunhofer scientists are exploring to what extent unwanted flavor properties are caused by new additives and are developing new strategies to avoid these.

The Fraunhofer scientists have many years of experience in sensory analytics. A well-trained sensory panel and a sensory analytics laboratory are available. Physiological investigations and *in vivo* monitoring complement the analytical equipment for the characterization of flavors. This means it is possible to assess the sensory contribution of specific ingredients, taking into account the complexity of food matrices.

Research and development in this area are not only focused on the characterization of existing flavors, but we also explore the formation of flavors from their respective precursor substances and their dependence on manufacturing and process parameters. Based on these results, the Fraunhofer Group for Life Sciences develops for its partners concepts to optimize the desired flavor impressions and to avoid the formation of off-odors.

Our expertise covers not only the original flavors of foods, but also the possibilities for optimally preserving these by means of tailored packaging systems.

3 *Intelligent packaging: film with integrated indicator*

3

A TRIO – PACKAGING, SHELF-LIFE, AND QUALITY

For all those involved in the food manufacturing process it is important to ensure a high level of food quality. This holds true not only for food manufacturers and filling companies, but also for the producers of packaging materials. Providing services to assess the quality status of foods and to identify the reasons for quality loss during storage are key areas of our work. We develop problem-specific analytical methods to determine quality parameters and the kinetics of quality changes in food products.

This is complemented in a very special way by our competence center for "Active and Intelligent Packaging". In this center we test the efficacy of active and intelligent packaging systems regarding, for example, their ability to preserve food quality, or their ability to monitor and indicate the condition of the packaged food or the package even during transportation and storage.

Intelligent packaging solutions

Polymer films with active functions such as oxygen scavenging or release of antimicrobial agents, sometimes in combination with indicator functions, are currently an important focus of our research and development activities. Oxygen indicators, for example, are able to indicate leaks in inert gas packaging, but also act as tamper-proof elements and so increase the safety of foods.

Depending on the packaged goods, there are different requirements for the barrier properties of the packaging material, such as gas and vapor permeability. During sterilization of ready-to-serve meals in plastic packaging (with an EVOH barrier layer), for example, the oxygen barrier of the polymer material is weakened, leading to the effect known as "retort shock". Oxygen scavengers integrated into the polymer can minimize the effects resulting from the reduction of the barrier function during the sterilization process.

As a matter of course, only preservatives approved for use in foods by the relevant authorities are employed in the development of antimicrobially active polymer packaging materials. The aim of this development work is not to introduce preservatives into the packaged food, but to achieve protection where it is required: on the outer surface of the foods. Traditional packaging films are coated with an active layer, from where very small amounts of antimicrobially active substances diffuse to the food surface and become effective there. Even very small amounts of an antimicrobially active substance can inhibit the growth of microflora on the food surface and are thus an effective link in the hygienic chain.

1 *Individual food formulation aimed at optimized nutritional value and stable texture*

FOOD PRODUCTS PROVIDING ADDITIONAL HEALTH BENEFITS

Leading food manufacturers have predicted increasing demand for foods which provide an additional physiological benefit. The development of such food products will become an important research area for the future of this sector. Top priority is the prevention of obesity and cardiovascular disease; other topics of high importance are the strengthening of the immune system and overall fitness. Nowadays, consumers are wanting more than ever before food constituents that support a healthy diet. However, healthy foods are not medications – and therefore consumers expect not only the promised contribution to a healthy diet, but also a pleasant taste.

Foods with optimized nutritional value

Many of our foodstuffs have a very high calorie density. Simply reducing their sugar and/or fat content will normally also reduce the sensory pleasure from eating this food product. Both the texture and taste impression will change decisively. The Fraunhofer Group for Life Sciences is developing optimized food formulations with reduced sugar and fat contents by using appropriate substitutes. Different ingredients (of natural origin whenever possible), for example fat substitutes based on vegetable proteins, when skillfully combined allow the calorie content to be reduced without adversely affecting the pleasure of eating the food or its digestibility.

Despite overnutrition in large numbers of the population, nutritional deficits also play a role in certain population groups. Elderly people, for example, often eat too little protein, and in many cases there is also a fiber deficit. Food products supplemented with additional nutrients are well suited to compensate such deficits. Supplementation with these ingredients may, in fact, change the texture of the food, however, this is taken into account accordingly during product development.

Formulations containing ingredients of vegetable instead of animal origin are also increasingly being demanded by consumers. This substitution also requires individual adjustments of the formulation, something the Fraunhofer scientists are able to do. Protein concentrates and protein isolates, which can for example be used for this purpose, can be manufactured on a pilot scale in standardized quality.

Bioactive food ingredients and functional food

Consumers are consciously making a decision in favor of food products with bioactive supplements and trust that the promised effect is delivered. In order to protect consumers, approvals for health claims are granted only if efficacy has been proven. This proof represents a new scientific challenge for our scientists. Completely new methods and test procedures have to be developed to enable initial proof of efficacy prior to the clinical trials.

2 *Oxygen measurement*

2

Research on bioactive substances begins with the detection and identification of novel ingredients of vegetable or marine origin. Sea fish in particular is considered to be a healthy food because it has a high content of essential amino acids and omega-3 fatty acids. The recommended daily intake of omega-3 fatty acids is currently about 500 mg. For patients with increased triglyceride levels, even three to four grams of omega-3 fatty acids per day are recommended. These large amounts are difficult to take in by eating fish, which is why corresponding capsules are offered as supplements. The omega-3 fatty acids they contain have so far been isolated from fish oil, a byproduct of fish meal production. Fish meal and fish oil, however, are also necessary to produce fish food for aquaculture. As aquaculture is one of the strongest growing sectors of the agro-industry, the price of fish meal and fish oil is likely to go up considerably in the future, and the demand for these products may pose a further threat to the already highly endangered fish stocks. Another important aspect concerns ensuring the quality of the fish oil. Lipophilic environmental pollutants readily accumulate in fish with a high fat content and must be removed with sophisticated methods during isolation of the omega-3 fatty acids so as to guarantee purity and meet safety standards. For many people, the strong inherent odor of fish oil capsules is also a reason for refraining from taking such dietary supplements.

This is the starting point for the research work of the Fraunhofer Group for Life Sciences, with the aim being to develop alternatives for the controlled manufacture and recovery of high-quality, low-odor dietary supplements.

For the production of eicosapentaenoic acid (EPA), which also belongs to the omega-3 fatty acids, an efficient manufacturing method based on algae has been developed. The marine microalga *Phaeodactylum tricomutum* is the starting point here. It is cultured in photobioreactors specially designed to assure optimal light supply to all algal cells via customized flow control. In addition, all relevant operating parameters, such as the components of the medium, have been optimized to meet all prerequisites for industrial EPA production. High growth rates, a high EPA content, and a manufacturing process which uses nothing but sunlight as energy source have thus been achieved. Likewise, importance has been attached to low production costs for the reactors.

Proteins and fibers with cholesterol-lowering effects are, for example, also recovered from vegetable raw materials. The definition of food formulations, food production procedures, and conditions for the storage of food is another important research topic, in order to identify the effect of these processes on bioactivity and to enable process optimization. The physicochemical behavior of the novel ingredients and their interactions with the food matrix are investigated in order to enable transfer of the desired physiological effect of the food to a wide range of different foodstuffs.

1

In vitro and *in vivo* proof of functionality

Validated *in vitro* tests can quickly provide results at low cost for the process of functionality testing. The development of *in vitro* tests with cell and tissue cultures to enable the physiological effects of novel food ingredients to be characterized is an active area of work of the institutes of the Fraunhofer Group for Life Sciences.

For absorption analyses, the standardized CaCo-2 test is available. For absorption, toxicity, and metabolism studies a three-dimensional vascularized intestinal model has been developed. This model is based on a matrix with a blood vessel equivalent (BioVaSc – Biological Vascularized Scaffold), on which intestinal cells and endothelial cells are cultivated physiologically – under conditions resembling those in the human intestine. Different parameters of this supply cycle such as flow rate, mass flow, pressure, and pulse can be computer-controlled and modulated. The 3D intestinal test system can be used to study the absorption, toxicity, and bioavailability of orally administered substances.

The influence of processing steps and storage conditions on the bioavailability and efficacy of the active ingredient can also be investigated in these *in vitro* systems. First statements about possible health claims can thus be made in a short space of time. The number of time- and labor-intensive intervention studies can thus be reduced; these *in vivo* tests can also be conducted by the Fraunhofer Group for Life Sciences in-house or in close cooperation with external clinics.

The Group closely collaborates with the responsible authorities and expert committees. At an international level too, the scientists engage in an intense exchange of ideas and experience, for example with the Japanese authorities, which issued regulations for the authorization of functional food as early as 1991.

Healthy pleasure

Functional food should not only be healthy but also tasty. Key factors for the success of a product in the marketplace, besides its proven health effects, are quality and the pleasure of eating it.

Flavor, most specifically taste and odor, as well as texture and mouthfeel are key aspects we also keep in mind when developing functional foods.

2

1 *Dried fruit produced by vacuum expansion*
2 *From sunflowers to functionalized food ingredients*

FOOD CHAIN MANAGEMENT – SAFETY FROM THE SEEDS UP TO THE FINISHED PRODUCT

The safety and quality of foods are becoming of ever greater interest to consumers and represent an important competitive aspect for companies operating in the food sector. Food chain management looks upon the food production process as an integral process and thus offers an optimal approach for ensuring food quality and traceability. It takes into account all the stages that a food product goes through, from the initial production via processing and retailing right through to the consumer.

"Food Chain Management" is also the name of a Fraunhofer alliance. A total of 10 Fraunhofer institutes from different Fraunhofer groups are collaborating in this alliance in order to carry out joint projects and translate the most recent scientific findings into products and solutions to solving these tasks.

A new approach in food chain management is also integrating the disciplines of microelectronics and logistics. This close dovetailing is spawning new competences and research approaches on a technological and also on a consumer-oriented basis.

The **Fraunhofer Food Chain Management Alliance** is thus well qualified to provide consulting and R&D services to major companies and small and medium-sized enterprises, and also to funding authorities and institutions at national, European, and worldwide levels.

For further information, please see:
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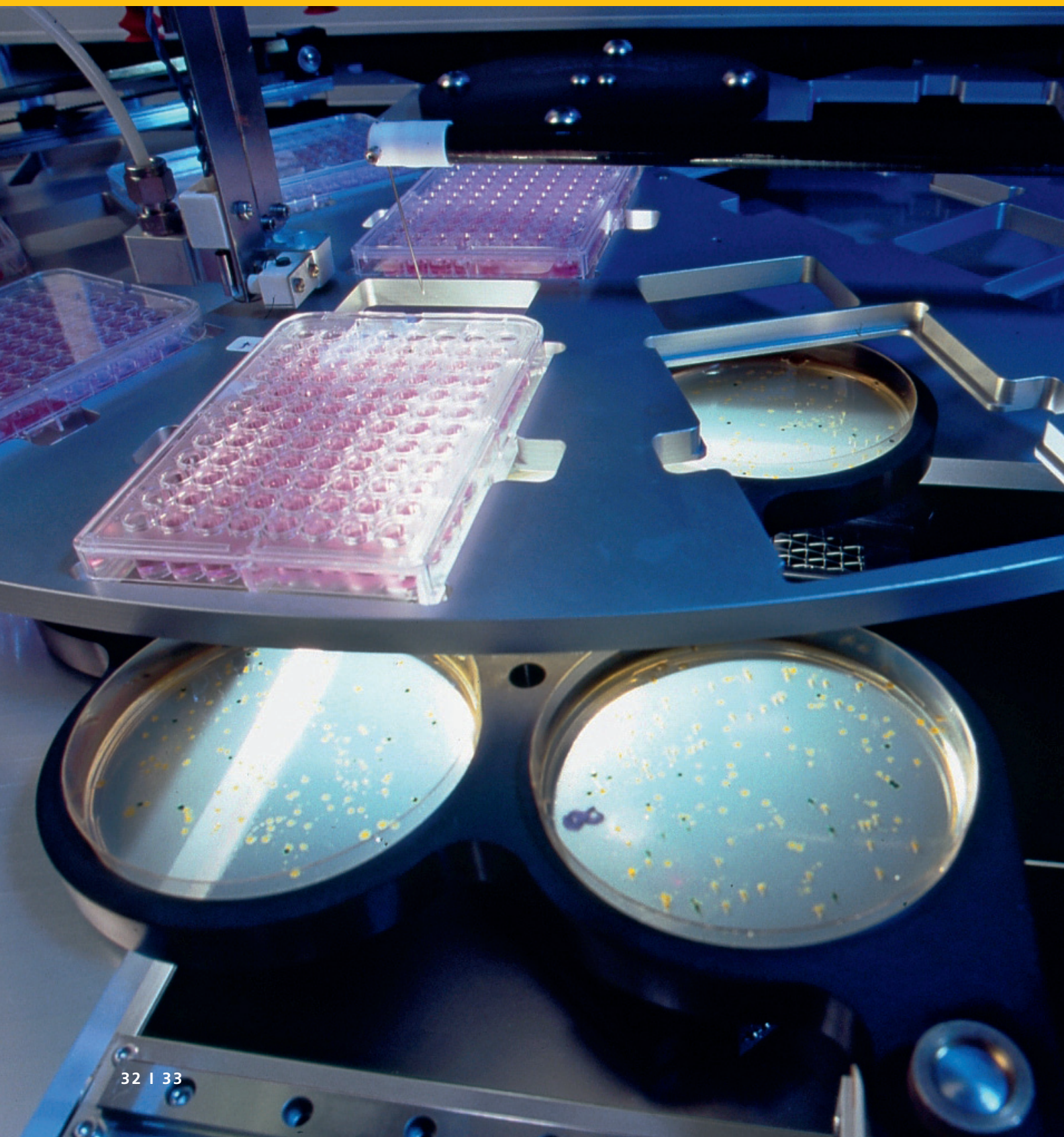
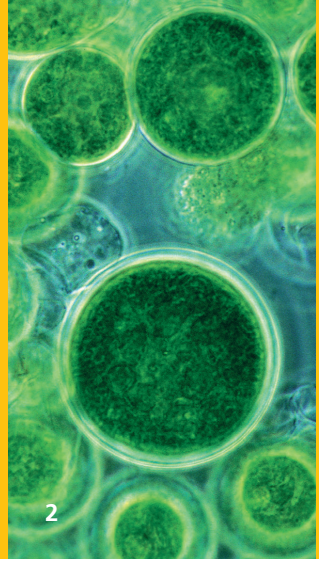
THE NEW POTENTIAL OF BIOTECHNOLOGY: THE CHALLENGE TO LEARN FROM NATURE FOR INDUSTRIAL EXPLOITATION



OVERVIEW

An increasing number of vegetable raw materials are becoming interesting as feedstocks for high-quality products. The refinement of these highly diverse raw materials requires completely new synthesis processes. Learning from processes occurring in nature, where complex reactions are single-step, enzymatic, and take place under mild conditions, the Fraunhofer Group for Life Sciences is developing novel biotechnology processes geared to the principles of "sustainable development" and "responsible care". The Group is laying the foundations to make sure that the required biomass is not only reliably available in the required quantity and quality, but also suits the requirements of the biotechnological manufacturing processes to the highest possible degree. One aim of the Fraunhofer experts is to transfer process steps into the plant production system. This would enhance the competitiveness of the final products. Blue biotechnology likewise occupies a fixed place in the services offered by the Group. Marine microorganisms – algae, bacteria, and zooplankton – are certainly interesting options for mass production of new materials. Enzyme-catalyzed reactions instead of the traditional synthesis paths can often substantially reduce the cost of production and waste disposal. The Group's potential to optimize existing enzymes and systematically search for novel enzymes is based on methods of, for example, genomics, metagenomics, and proteomics. Enzyme optimization for industrial use is achieved by means of molecular evolution and combinatorial libraries.

This know-how is particularly beneficial for research in the new domain of yellow biotechnology, i.e. insect biotechnology. In this area, a so far unknown number and variety of new enzymes and antibiotic substances are providing the impetus for intensive research activity. Completely in line with the sustainability concept, the Fraunhofer Group for Life Sciences will search for new possible uses for residues from the food industry, agriculture, and forestry for its clients, including development of the required processes up to pilot scale. In the near future, the critical step from the laboratory to industrial application will be supported by the Fraunhofer Center for Chemical Biotechnological Processes, Leuna, Germany. The concept of this biorefinery is highly flexible, allowing a wide range of different raw materials, according to requirements, to be used and tested as feedstocks for chemical products.



1 *Airlift photobioreactor*
2 *Microalga Haematococcus pluvialis*

RENEWABLE RAW MATERIALS AND VALUABLE RESIDUES

Surging crude oil prices and crises in the petroleum-producing countries have increased people's awareness of dependence and of the finiteness of our natural resources. The consequent search for novel raw materials for industry has led to surprising results, showing very impressively that nature's diversity is far from having been completely exploited. Furthermore, in view of ever more stringent regulations and the worldwide quest for sustainable development, the design of sustainable industrial processes in the chemical, pharmaceutical, and food industries is becoming more and more important.

Biomass is the only alternative to fossil raw materials for the manufacture of chemical and pharmaceutical products. Plants with their enormous diversity offer a broad range of potential raw materials. Photosynthesis leads to a huge spectrum of widely differing chemical compounds, which so far have only been partially exploited. A particularly interesting option is the use of these renewable raw materials as chemical intermediates for polymers and special chemicals. A challenge for the future is to expand the industrial use of raw materials from plants, while at the same time safeguarding the production of food and animal feed and protecting areas of unspoiled nature.

In order to improve and increase the industrial use of bio-based raw materials and biotechnological processes, new approaches for research, development, and manufacturing are required: approaches geared to the general principles of "sustainable development" and "responsible care".

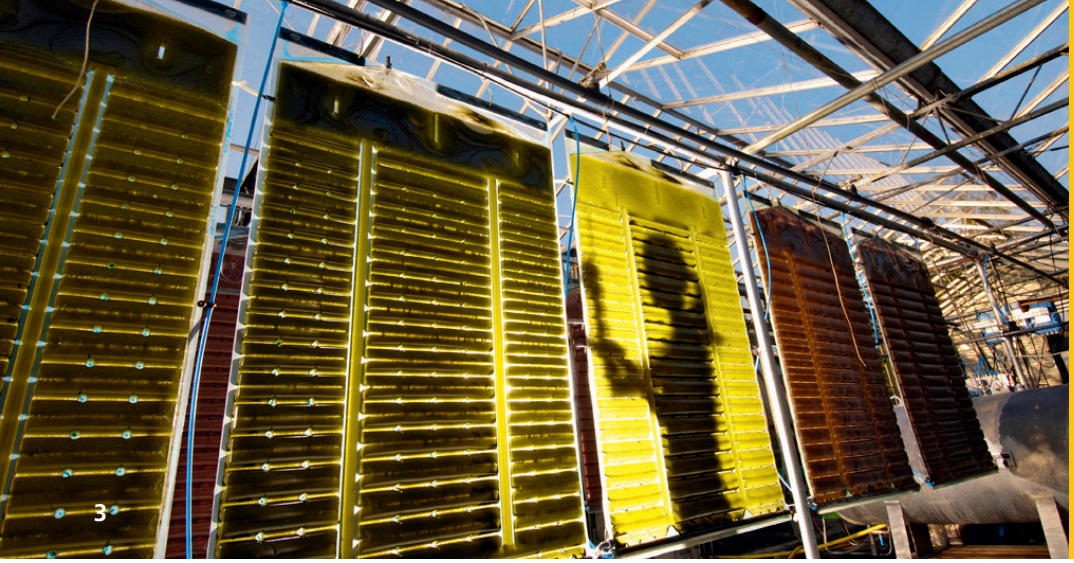
For the use of renewable resources, the product tree is a lot more branched than that for the mineral oil-based line. Synthesis processes taking place in nature can be exploited, for example, by isolating and, if need be, modifying individual fractions of renewable resources; another path using enzymatic biodegradation leads to platform products – the base products for biotechnological or chemical syntheses.

Both these possibilities for exploring new sources of raw materials are being intensively studied by scientists in the Fraunhofer Group for Life Sciences.

White and green biotechnologies going hand in hand

The content of valuable components in a plant for use in industrial biotechnology depends on the type of plant and on its treatment by the grower.

The basis for targeted improvement of a plant's properties includes systematic analysis of its metabolic pathways and comprehensive knowledge of its ingredients and their respective properties. This has been facilitated by technological progress in functional genomics, proteomics, and metabolomics. The efficiency of biotechnological manufacturing processes in industry can be increased by tailoring the plants which provide the raw material to the particular manufacturing process. Matching the plant properties to the technological and commercial requirements enables specific and broader use of biogenic raw materials for industrial biotechnology. A transfer of process steps into the plant as a production system is another option. Both approaches are being pursued within the Fraunhofer Group for Life Sciences.



3 *Pilot plant with 180-liter photobioreactors for culturing algae*

Blue and white biotechnologies acting together

The industrial production of novel ingredients by using marine organisms will become more and more important in the future. Marine organisms will be employed not only for the identification of such new ingredients, but will also be put to use for mass production. In this context, marine microorganisms such as single-cell algae or bacteria are of particular interest, as too are zooplankton or cultures of cells isolated from marine organisms. The Fraunhofer Group for Life Sciences is in a position to maintain the corresponding organisms and to develop and offer special customized reactors for this purpose.

Productive use of valuable residues

Besides the targeted search for plants as sources of alternative raw materials, researchers in the Fraunhofer Group for Life Sciences have an interest in plant residues from the food industry, forestry, and agriculture. These often still contain valuable compounds such as proteins, fibers, oil, or phytochemicals, which can be further exploited. For further use in technical applications, they first have to be isolated using appropriate methods with preservation of their valuable properties. We have wide experience in the fractionation of different vegetable raw materials and vegetable residues from the food industry. The development of fractionation processes on a laboratory scale and also the scale-up to pilot scale are among the services offered by the Fraunhofer Group for Life Sciences.

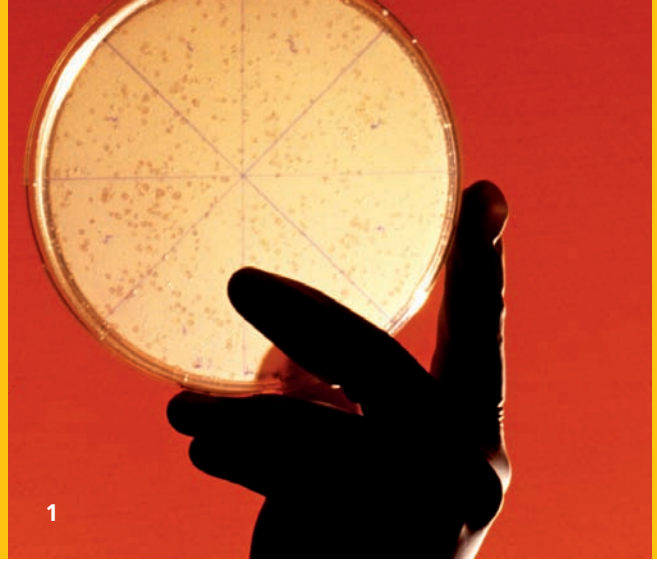
In many cases, modification of proteins and other vegetable raw materials prior to their technical or energetic use can contribute to achieving the desired physico-chemical properties. The Fraunhofer Group for Life Sciences develops innovative processes for the chemical and, in particular, biotechnological modification of useful plant fractions, to enable high-quality and low-cost substitution of petroleum-based products.

Sustainable ways to products with multiple benefits

Like higher plants, microalgae bind atmospheric carbon dioxide and produce a large variety of valuable chemical compounds such as dyes, unsaturated fatty acids, and active pharmaceutical ingredients via photosynthesis. They grow faster though, and have higher productivity than plants on land. This makes them an interesting alternative source of raw materials for industrial, white biotechnology.

Already today, native and modified biogenic raw materials are used in many different sectors: applications range from energetic uses as solid and liquid fuels to industrial uses as lubricants, adhesives, and coating materials. Due to our many years of experience and comprehensive expertise, the Fraunhofer Group for Life Sciences is a competent and attractive partner for the development, characterization, and industrial implementation of these innovative products.

1 *Enzyme screening: DNA of soil microorganisms is expressed in laboratory strains*



ENHANCED RANGE OF RAW MATERIALS FOR BIOTECHNOLOGICAL PROCESSES

The main tasks in the biotechnological area are to make available low-cost substrates and to develop new or improved enzymes. Further challenges are to develop new biotechnological processes and optimize existing ones, to couple these with chemical processes in order to achieve process integration, and to develop new processing methods and optimize existing ones.

Biotechnological processes use sugars as a carbon source, obtained either directly from plants or created from starch-containing plants by hydrolysis of polysaccharides. In view of the worldwide debate about the competing use of sugar- and starch-containing plants for industrial purposes, it is becoming increasingly important to make available alternative raw materials for fermentation based on lignocellulosis. The institutes of the Fraunhofer Group for Life Sciences are investigating and developing novel enzymes and methods for substrate digestion based on lignocellulosis.

New biocatalysts

Microorganisms and their enzymes are of major importance for the manufacture of chemical and pharmaceutical products using biotechnological methods. New applications, for example the recovery or modification of special chemicals, require new or improved enzymes. Enzymes as bio-catalysts offer the benefit of high substrate specificity and stereo-selective reaction. This makes them attractive for technical industrial solutions such as the synthesis of enantiopure products or intermediates. The use of enzymes frequently allows substantial cost reductions both in production and waste disposal processes. Furthermore, this process technology opens up completely new market opportunities. In fact, it is often enzymes that make it possible for certain products to be manufactured at all.

The search for microorganisms and their enzymes involves traditional methods, but also innovative methods such as the complete screening of genes or proteins, which is referred to as genomics, metagenomics, and proteomics.

2 *Picking robot*

3 *Process development to enable the use of lignocellulosis-based raw materials and residues*

In order to develop efficient and low-cost processes, the Fraunhofer researchers are concentrating on the following:

- Identification and characterization of new or improved industrial enzymes, in particular by establishing culturing methods for microorganisms which to date have not been able to be cultured
- Optimization of enzymes suitable for industrial use by molecular evolution and combinatorial libraries
- Development of manufacturing and purification processes for recombinant technical enzymes
- Immobilization of enzymes and coupling of biocatalysis and chemocatalysis

Experts reckon that the percentage of microorganisms which have not yet been able to be cultured is about 99% of the whole population. To enable this promising genetic resource to be used, Fraunhofer researchers in cooperation with partners from industry have set up metagenomic gene libraries based on environmental samples. For this purpose, they isolated the microbial DNA directly from the environmental sample and introduced it into a cultivable host species.

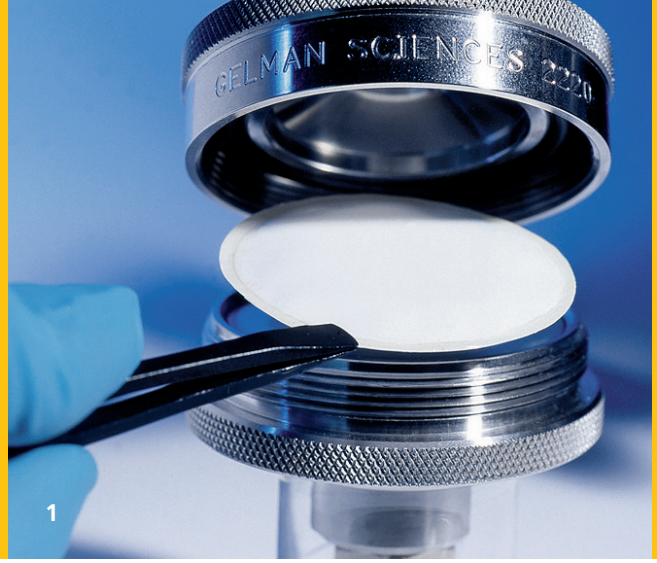
Metagenomics as an advanced level of genome research in prokaryotes systematically provides access to the whole complexity of genetic information obtained from microbial communities. By means of high-throughput assays, the gene libraries can be screened for desired enzyme activities. Using this method, a large number of enzymes have already been identified which were not in the known databases and thus can now be used without limitations.

Furthermore, the genomic information obtained in sequencing projects is used systematically in the Fraunhofer Group for Life Sciences in order to isolate novel enzymes for technical applications.

Enzyme diversity of yellow biotechnology

Insect biotechnology, also referred to as yellow biotechnology, is a promising research area of the Fraunhofer Group for Life Sciences. Insects are the organisms having the highest biodiversity. Four to six million species of insect exist, compared to only about 250,000 plant species. The evolutionary success of insects is due on the one hand to the large variety of antibiotic substances which provide effective protection against infection, and on the other hand to a large variety of enzymes which help them exploit almost any organic material as a food source. The exploration of this diversity of molecules occurring in insects and the systematic exploitation for red, green, and white biotechnology is a challenge for researchers.

The enormous diversity of enzymes which enables insects to use almost any organic material as a food source represents another very interesting resource for white biotechnology. Due to their novel properties, these may help open up new or expanded application areas, make methods of synthesis more economic, and enable material or energy recovery from waste material which hitherto has been used insufficiently or not at all.

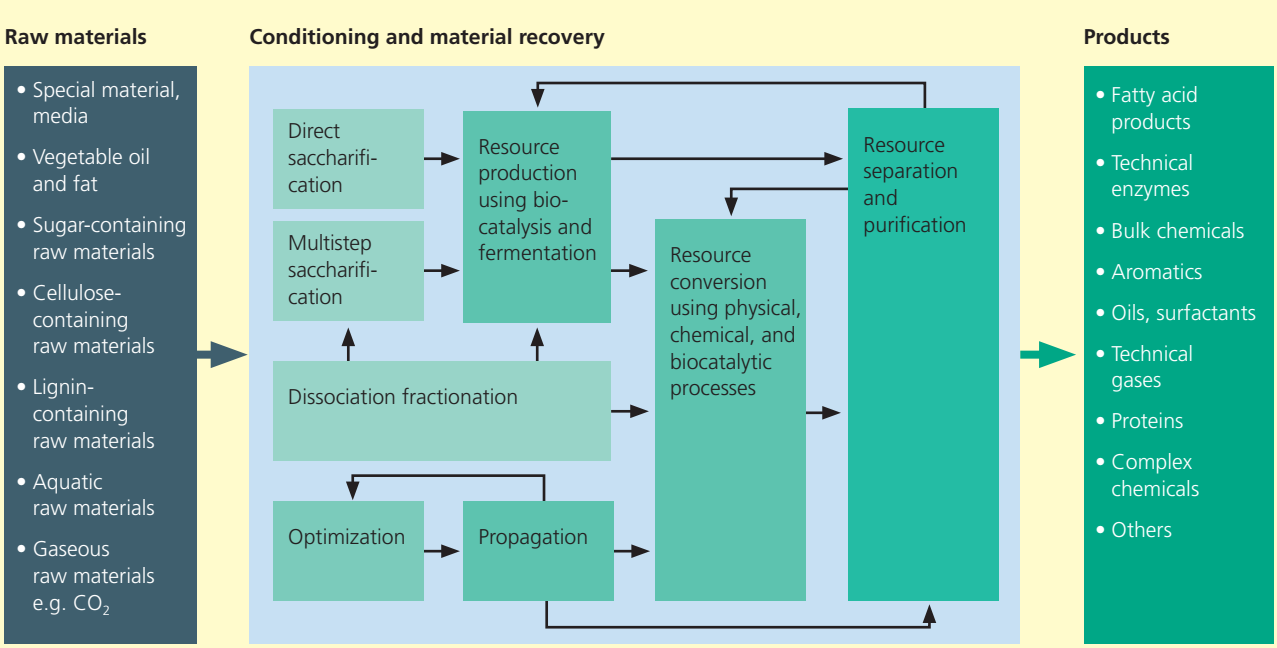


1 *Composite membrane with functionalized nanoparticles to enable selective separation processes*

Process development for fermentation and downstream processing

High demands on product quality and a renaissance of natural materials for industrial applications require new and efficient production and processing methods. The Fraunhofer Group for Life Sciences is an attractive partner in this regard, thanks to its expertise in process development for biocatalysis, fermentation, and downstream processing as well as in upscaling up to pilot scale. It develops solutions for optimized fermentation and for the isolation, separation, and purification of biotechnical products using mechanic and thermal separation techniques. Membranes and membrane processes in particular are applied, because these processes can be used specifically to suit the particular chemical and physical properties of the product (size, charge etc.). Examples are membrane filtration, electrodialysis, and combinations of membrane with conventional separation techniques or with powerful chromatographic methods.

Scheme 1: Renewable raw materials for chemical products



Source: Fraunhofer IGB

2 *Integrative biorefinery concept: make complete use of renewable raw materials*

FRAUNHOFER CENTER FOR CHEMICAL BIOTECHNOLOGICAL PROCESSES, LEUNA

Petroleum is a highly coveted feedstock for numerous products such as plastics, lacquers, detergents, adhesives, and cosmetics. Its availability, however, is limited. Renewable raw materials such as straw, wood, microalgae, and many others have the potential to replace petroleum. Chemical companies all over the world are working to develop novel processes. Today, however, the use of renewable raw materials on an industrial scale is still a financial and technological challenge for companies.

Aiming to support the critical step from the laboratory to industrial application, the German *Land* Saxony-Anhalt, the German federal government, and the Fraunhofer-Gesellschaft have been planning to set up a chemical biotechnological process center which is now being established as Fraunhofer Center for Chemical Biotechnological Processes CBP at the German chemical industry center Leuna. The biorefinery concept, which can be used very flexibly, will offer innovative possibilities for the future use of biological raw materials based on oils and fats, cellulose, and of starch- or sugar-containing raw materials as precursors for chemical products. This will allow the development of new products and processes involving industrial biotechnology up to the point that they are ready for industrial use. The CBP will thus contribute to reducing our dependence on fossil fuels and to reducing carbon dioxide emissions.

By providing the required infrastructure and pilot plant/mini-plant facilities, the Fraunhofer CBP will enable cooperation partners from research and industry to develop and scale up biotechnological processes for the use of renewable raw materials up to industrial scale. Seven process plants for process development and scale-up will be set up consecutively.

A first biorefinery pilot plant, which will allow the main constituents of wood (cellulose, hemicellulose, and lignin) to be chemically recycled, is scheduled to become operational in the Leuna facility by the end of 2011 as part of the lignocellulose biorefinery project. The initial substrate is waste wood, which first needs to be separated efficiently into its individual components and split up into sugars and phenols. The resulting sugars will be transformed by bacteria into elementary chemicals, which can then be used to produce plastics such as polyethylene. The phenols obtained from the wood constituent lignin will prospectively be used for the production of adhesives or as feedstock for chemical syntheses. Any residues from this process can be used for energy and biogas production – thus completing the utilization of the initial substance "wood".

A critical factor for the success of the biorefinery concept is collaboration with partners from industry from the very beginning: more than 20 industrial partners are involved in different projects already today. For every project, the industrial partners perform economic and ecological sustainability analyses. The design and conception of the different plants in each case allows a comprehensive efficiency analysis that can be extrapolated to large-scale production situations. In fact, this provides ideal preconditions for technology transfer.

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PROCESS, CHEMICAL, AND HERBICIDE SAFETY: THE CHALLENGE OF ENVIRONMENTAL AND CONSUMER PROTECTION

OVERVIEW

New laws and regulations such as REACH as well as a growing sense of environmental awareness have led to an increased demand for expert assessment and appraisal of new and existing substances. In order to reconcile people's need for safety, legal assurance, and economic efficiency, costly analytical investigations must be planned with care. By considering exposure and environmental scenarios and structure-activity relationships, the Fraunhofer Group for Life Sciences can establish the first outline data. The large variety of data pools to which the Group has access thanks to its networked structure is of particular benefit here. Besides the traditional test methods in compliance with GLP and in accredited laboratories (DIN EN ISO/IEC 17025), the Group can also perform complex environmental simulations such as fate studies and micro- and mesocosm studies for the assessment of plant protection products.

Using new powerful screening methods such as *in vitro* tissue models or high-throughput systems for toxicological *in vitro* tests, the Group is paving the way: more safety with fewer animal experiments. The Group's fish cell lines, for example, offer a promising alternative to conventional fish tests. The debate about the potential risks to man and the environment resulting from nanotechnology is still ongoing. The Fraunhofer Group for Life Sciences utilizes all its expertise to achieve quick assessments.

A properly functioning water supply and disposal system is an essential requirement for any civilization. This covers the supply of clean drinking water and the hygienic disposal of wastewater. The result of DEUS 21, a research project in which the Group has played a pivotal role, provides an interesting model for efficient wastewater disposal – a decentralized solution without complex piping networks which can be adapted to local requirements. The on-line broadband sensor AquaBioTox means the Group is contributing to increasing the safety of drinking water.


1

TESTING AND ASSESSMENT OF CHEMICALS

As a consequence of various EU directives, current German legislation requires the thorough testing of chemicals and biocides, including substances that are already in the marketplace. The European REACH policy (Registration, Evaluation and Authorisation of Chemicals), for instance, will necessitate extensive investigations on industrial chemicals in the years to come.

Consulting and support

The Fraunhofer Group for Life Sciences can advise you from the very beginning through to successful project completion, in all phases of chemical testing and assessment. Following a structured plan of the process, we proceed step by step towards the goal. In doing so, we utilize and link existing knowledge from a wide variety of data pools as a first important step towards filling data gaps. We have many years of experience in developing substance-specific strategies for generating valid data for uncovered endpoints. For this purpose, we resort to the evaluation of structure-activity relationships (QSAR), read-across, and chemical categories and analogy concepts. We use exposure scenarios to describe the ways in which there can be exposure to a chemical; this enables us also to clarify whether exposure waiving – that is, the non-carrying out of certain studies due to the fact that there is no relevant exposure – can be applied. Environmental scenarios provide information about the behavior and fate of the chemical substance in the environment. All steps of this process are aimed at minimizing subsequent experimental studies.

Traditional methods

The Fraunhofer Group for Life Sciences offers combined expertise in toxicology and ecotoxicology as well as laboratory testing capacity and has many years of experience in traditional methods for substance testing. Exposure to different groups of chemicals and their toxicological and ecotoxicological hazards are thus tested and evaluated by the Group in accordance with international guidelines. The tests are performed in compliance with GLP regulations or in accredited laboratories (DIN EN ISO/IEC 17025). Expert reports and dossiers are prepared and a final risk assessment is compiled. Where the available data is insufficient, the Fraunhofer Group for Life Sciences develops testing strategies, scientifically supervises the tests, and performs the necessary analyses required for registration.

Innovative screening methods

Depending on the type of substance and the scope of testing, traditional methods are often too costly. The Fraunhofer Group for Life Sciences develops novel procedures that save time and costs, in particular in the fields of chemical risk assessment and substance property screening. Existing exposure models for human beings and the environment are enhanced and databases for structure-activity relationships created. In addition to the competencies offered in the areas of structure-activity relationships (SAR) and inhalation toxicology, the Fraunhofer Group for Life Sciences establishes, for example, *in vitro* test models. These allow basic toxicological data to be obtained without animal experiments. The three-dimensional *in vitro*

1, 2, 3 *Consulting and support from the registration process through to product authorization*

2

3

tissue models possess many typical properties which are characteristic of the corresponding organ in the organism. Cell-biological and molecular-biological analyses of the toxicity of chemicals, for instance of cell toxicity, genotoxicity, and embryo toxicity, can be performed close to the real-life situation. A certified *in vitro* skin model allows the skin penetration by chemicals to be mimicked, and it can also be used for toxicity tests. Coupling 3D cellular spheroids with a capillary chip even allows high-throughput systems for toxicological *in vitro* tests.

Validated fingerprints obtained by gene expression analysis allow the potential for inducing chronic and in particular also carcinogenic effects to be reliably estimated.

Marine ecosystems – development of alternative methods for the testing and risk assessment of chemicals

The increasing introduction of pollutants into the environment by man represents a considerable hazard for marine habitats. The ever growing number of chemical compounds getting into the sensitive ocean ecosystem makes it necessary to obtain information about the potential toxic effects of substances on marine organisms.

Over recent years, *in vitro* toxicity tests in cultured fish cells have become increasingly important. Primary fish cells and permanent fish cell lines not only represent an excellent alternative to traditional tests in fish (*in vivo* fish assay according to the German standard DIN 38412) in aquatic (eco-)toxicology, but furthermore offer the possibility to investigate the mechanisms of toxicity of chemical compounds. The Fraunhofer Group for Life Sciences has already established several fish cell lines and has gathered expertise in this domain. Fish cell cultures possess great self-renewal ability and are therefore highly suitable for use in *in vitro* toxicity tests, in particular for investigating toxic substances which accumulate in the marine food chain. Compared to corresponding long-term cultures of human and murine cell lines, fish cell lines exhibited higher sensitivity to environmentally relevant toxic substances that are introduced into waters.

For further information about the testing and risk assessment of chemicals under the European chemicals policy REACH, please refer to the "REACH Consultancy and Support" brochure of the Fraunhofer Group for Life Sciences.

1 *Agricultural use of plant protection products*

AUTHORIZATION OF PLANT PROTECTION PRODUCTS

Plant protection products are necessary for economically sustainable agriculture, but on the other hand, their ingredients may pollute the environment. In order to maintain the ecological balance and protect human health, it has to be ensured that any effects on ecosystems are only of a minor and temporary kind.

Minimization of uncertainties in the assessment

The Fraunhofer Group for Life Sciences tests and assesses plant protection products according to national and international regulations on plant protection. Besides standardized testing procedures to determine intrinsic substance properties, the Fraunhofer scientists also use complex environmental simulations. The experimental focuses include fate studies (e.g. lysimeter studies), micro- and mesocosm studies, fish full life cycle studies, and species sensitivity distributions. The scope of services is complemented by exposure and effect modeling, expert reports, and consulting. The Fraunhofer Group for Life Sciences identifies and quantifies risks and minimizes assessment uncertainties (higher tier risk assessment). By integrating these methods early in the product development process, unnecessary development costs can be avoided. The Group also looks upon itself as a scientific intermediary between industry and authorities.

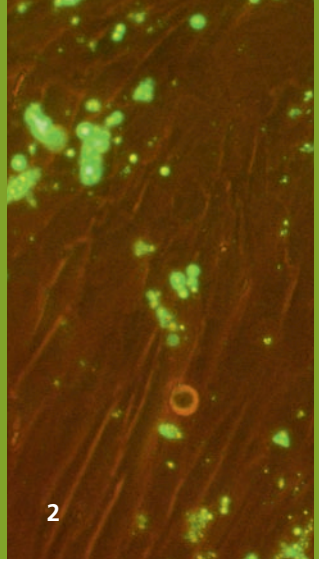
Metabolism studies

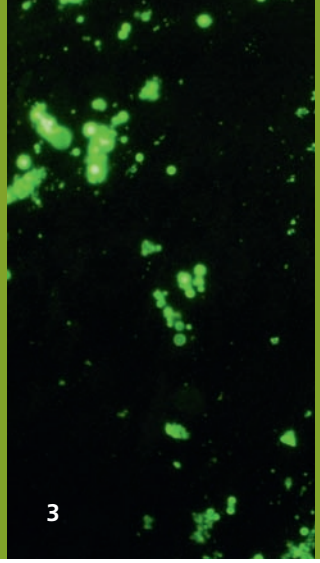
Authorization of a plant protection product requires not only information about the active ingredient, but also data on degradation and reaction products (metabolites). Studies to this end are performed in relevant plants and in productive livestock; the residue analyses also have to include processing studies so as to get insight into the impact of treatment and processing on the crop or foodstuff. In addition, it has to be elucidated whether the active ingredient remaining in the soil will be absorbed and metabolized by or accumulate in subsequent crops.

A major challenge in such studies on the metabolism of plant protection products in soils, plants, and productive livestock is the elucidation of the chemical structure of the degradation products. For this purpose, the Fraunhofer Group for Life Sciences has at its disposal state-of-the-art analytical equipment including high-resolution MS and LC-NMR. Metabolism studies can be performed in open-land facilities, greenhouses, or climate chambers. The spectrum of plants that can be used ranges from field farming plants that are common in central Europe via vegetable and fruit cultures through to cultures of subtropical agricultural crops such as peanuts, cotton, and rice. Depending on the precise issue to be investigated, different soils can be used; the Group always has access to reference soils accepted by the authorities.

In the area of animal metabolism, the Group currently offers studies regarding metabolism and bioaccumulation in fish. Wherever possible, metabolism studies are performed by using cell cultures or modeling. In collaboration with its partners, the Group will in the future also be able to offer metabolism studies on farm animals.

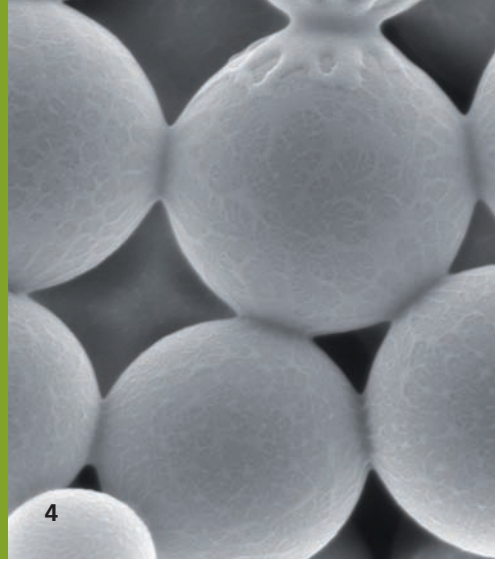
All studies can be performed with ^{14}C-labeled materials and in compliance with GLP guidelines. Many years of experience enable us to customize the test systems to our clients' specific requirements.





2, 3 *Pancreatic stem cells – uptake of nanoparticles differs between cell types*

4 *Nanoparticles viewed with a scanning electron microscope*



RISK ASSESSMENT OF NEW TECHNOLOGIES

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 in good time.

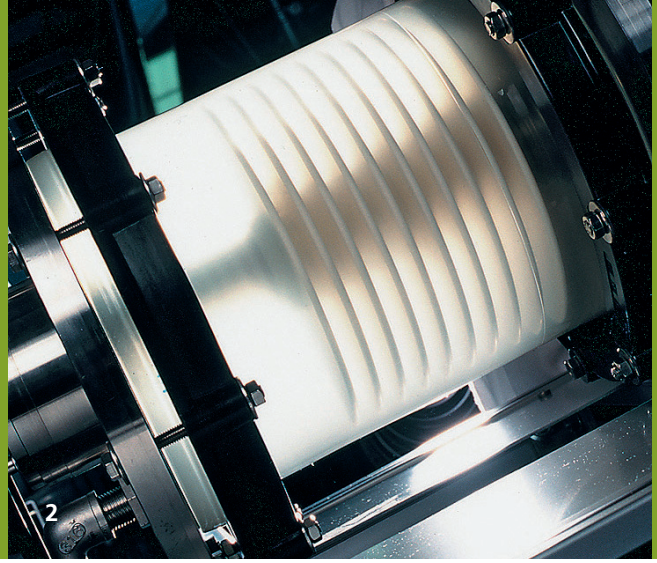
The wide spectrum of possible applications in medicine, environmental protection, packaging technology, production engineering, and the economic potential make nanotechnology a truly compelling field of research and motivate mankind to exploit the benefits. Past experience, however, has shown that technological 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, for example, what happens to nanoparticles when they enter the human body or the environment?

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.

A high degree of safety in the field of nanotechnology can be achieved by developing preventive recommendations. In this regard, the Fraunhofer scientists are acting according to the precautionary principle – for the sake of man and the environment.

For further information about nanotechnology research in the Fraunhofer Group for Life Sciences, please refer to our brochure entitled “Nanotechnology Research for Man and the Environment”.



WATER MANAGEMENT

In Europe, the development of a properly functioning wastewater disposal system allowed the great epidemics to be overcome. And even though the human right to have access to safe drinking water has not been legally stipulated, the international debate has made clear the essential role of water as a comestible product. The researchers in the Fraunhofer Group for Life Sciences are contributing to ensuring that this basic need can be met in a safe, humane, and environmentally compatible manner even during times of increasing demand.

Wastewater disposal to protect man and the environment

Besides containing inorganic and organic contaminants, wastewater also contains pathogens which, if inadequately treated, will be spread via the material cycles and may lead to outbreaks of disease. In industrialized countries, high-tech solutions are available in many domains and these are mostly implemented in centralized systems and treatment plants. The quality standards are very high, but operation and maintenance of these systems also involves considerable costs, which are passed on to the users and hence society. An enormous cost factor is the highly branched network of pipes. Their maintenance costs a fortune, and substantial effort is required to ensure contaminants do not get into the drinking water supply network and to prevent contamination of the environment by wastewater. However, despite the large effort that is required, maintenance and repair are normally well managed.

If, however, an unforeseen incident occurs within such centrally organized and complex structures, the consequences could be beyond control, in particular in large and growing cities. In decentralized supply and disposal systems, failures and disturbances can be localized faster, and unwanted or detrimental impacts can be limited by appropriate measures.

Decentralized systems are manageable, and with the common control systems that are nowadays in use they can be operated by significantly less staff than would have been possible only a few years ago. The research project DEUS 21, which is funded by the German Federal Ministry of Education and Research, initiated and coordinated by the Fraunhofer ITEM, and performed in collaboration with partners from industry, has shown that decentralized systems, when customized to the specific requirements of a particular location, can treat wastewaters very efficiently and safely in small quantities (Scheme 2).

Monitoring of water infrastructure systems

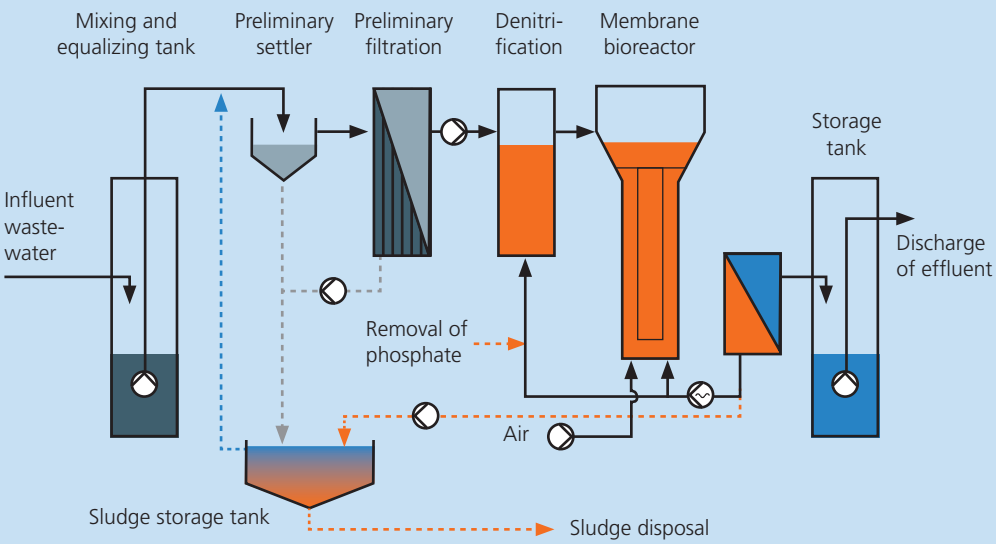
In Germany, sewage treatment plants as well as drinking water purification plants are subject to routine monitoring to ensure that they comply with the legal requirements for consumer protection. Drinking water is regarded as a comestible product and thus requires particularly careful monitoring. This is currently achieved by routine sampling and comprehensive chemical and microbiological analyses of the drinking water samples. German drinking water suppliers have to satisfy the high quality standards of the national Drinking Water Ordinance (2001, 2006).

1 *Ground water purification using a trickle-bed reactor*
2 *Rotating disk filter*
3 *Microcosms*
4 *Mesocosms*

The methods used for routine examination of in particular the piping network are in most cases rather time-consuming. Measurement methods which indicate unforeseeable incidents such as accidental or deliberate contamination that poses a threat to the water supply networks are vital so that immediate action can be taken to avert danger.

In the Fraunhofer Group for Life Sciences, Fraunhofer experts in information and data management are working with users and manufacturers of measurement devices for water body monitoring to develop sensors suitable for on-line monitoring. The higher safety standard thus achieved allows drinking water suppliers to respond quickly in the event of contamination of the drinking water. The AquaBioTox project, funded by the German Federal Ministry of Education and Research, has its focus on a broadband sensor. As the core element of this system, it combines microbiological and mammalian cell systems with a daphnia toximeter and with physico-chemical measurement parameters and reports any incidents or malfunctions to a decision-maker, who can then promptly initiate appropriate actions.

Scheme 2: Decentralized wastewater treatment plant



Example of a decentralized wastewater treatment plant in Heidelberg-Neurott, Germany: the purified effluent is subject to a filtration process prior to being discharged into the adjacent water body.

Source: Fraunhofer IGB

1 *Water – a scarce resource*

SUSTAINABILITY AS A GUIDING THEME

How can we achieve the aim of "preserving for ourselves and our children a natural basis of life that is viable for the future"?

The challenges we are currently facing are tremendous: climate change, water shortage, loss of biodiversity, soil degradation, and shortage of energy and raw materials. Pure relinquishment strategies are neither workable nor would they meet with public acceptance. Increasing ecological, economic, and social challenges require a system-oriented approach which promotes interdisciplinary thought and collaboration in order to develop innovative solutions. The basis is a perspective which integrates future requirements and demands with consideration of global justice. Research and development play a key role in achieving these goals. The focus is on innovative developments meeting the requirements of sustainable development. Future growth, taking into account the quality of life, must be achieved with only a fraction of our current resource consumption and a substantial reduction in emissions.

Sustainability is the word of the moment. But what exactly does it mean?

The term was coined by Hans Carl von Carlowitz in a forestry context as early as 1713 in his book "Sylvicultura oeconomica". This shows that mankind already recognized ecological limitations at an early point in time. An overall characterization of the term sustainability is provided in the definition framed by the Brundtland Commission (World Commission on Environment and Development – WECD) in 1987, which describes "sustainable development" as "development that meets the needs of the present without compromising the ability of future generations to meet their own needs". Intragenerational as well as intergenerational justice is thus the key concept of sustainable development. Sustainability is not a term that can be unambiguously defined in the sense of the natural sciences, but is rather a guiding principle of a normative nature. It describes a certain relationship between man and the environment which provides for the needs of both present and future generations.

The Fraunhofer-Gesellschaft's commitment to contributing to sustainable development has already been enshrined in its mission statement: "The Fraunhofer-Gesellschaft supports efforts directed toward the sustainable development of society, industry, and the environment. The Fraunhofer institutes play an active part in such efforts through a responsible approach to the implementation of new technologies and through research and studies conducted on behalf of industrial and public-sector clients."

Currently addressed sustainability topics cover: bio-based raw materials, raw material efficiency and resource management, water management, sustainable products and processes, climate change and cultural heritage, life cycle management and environmental assessment, renewable energy sources, energy efficiency, and energy systems, sustainable mobility.

We are implementing the sustainability concept in all our research activities; because sustainable development leads to innovation processes in industry and society and to the safeguarding of our natural basis of life.

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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. Dr. Uwe Heinrich
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