



**Fraunhofer** Institut  
Molekularbiologie und  
Angewandte Oekologie

Delivering Innovative Solutions  
in Applied Life Sciences throughout  
the World



## Profile of the Fraunhofer IME



## Profile of the Fraunhofer IME

### Our Focus Areas

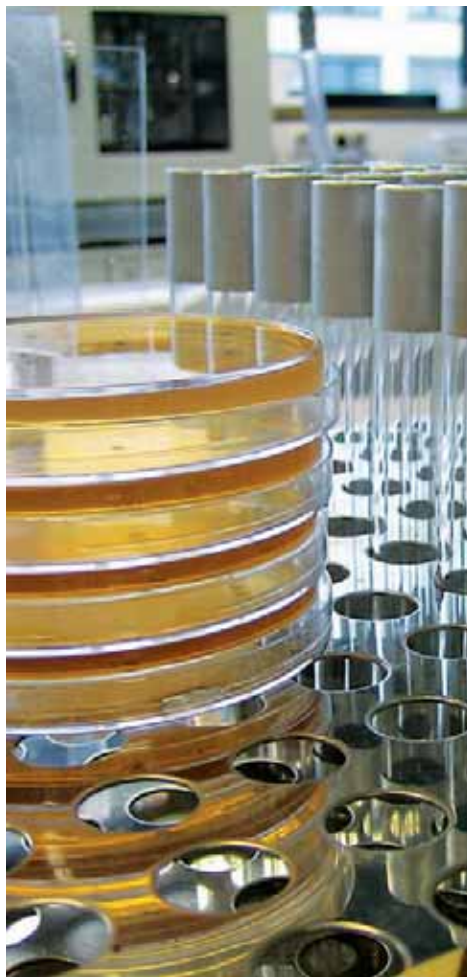
The Fraunhofer IME is a leading institute in the field of applied life sciences, delivering cutting edge research and development services throughout the world. As a part of the Fraunhofer-Gesellschaft, the IME is one of 56 Fraunhofer institutes found in more than 40 locations throughout Germany. These institutes conduct research that can be applied directly to public and private enterprises in industry, the service sector and public administration. In particular, the IME performs research and development projects in the fields of medicine, agriculture and environmental protection, and focuses particular attention on the following areas: the diagnosis and treatment of human, animal and plant diseases; the protection and improvement of food and feed stock; and the identification, assessment and reduction of risks in synthetic and biogenous substances for consumers and the environment.

### Our Greatest Resources

The IME is divided into three divisions at different locations. The Molecular Biology Division is located in Aachen, the Applied Ecology Division is situated in Schmallenberg and the Center for Molecular Biotechnology (CMB) is in Newark, Delaware, USA. We have 200 highly-trained

staff, more than 80% of whom are qualified scientists, engineers, technicians or other specialists with backgrounds in such diverse fields as genomics, ecology, ecological chemistry, biotechnology, molecular biology and pharmacology. Scientific expertise is, therefore, one of our greatest resources, but another is our state-of-the art facilities, including modern laboratories and a certified GMP facility for the production of recombinant proteins. Our interdisciplinary approach allows us to offer an extensive range of research and development services that support and encourage economic development while promoting social welfare and environmental stewardship.





## Our Leadership Promotes a Spirit of Collaboration

Professor Dr. Rainer Fischer is the Senior Executive Director of the Fraunhofer IME and Fraunhofer CMB, as well as full professor at the Institute for Molecular Biotechnology at North Rhine-Westphalia Technological University in Aachen (RWTH). Under Prof. Fischer's leadership, the IME collaborates closely with the RWTH in research and also offers a research-driven educational program.

Through the Fraunhofer-Gesellschaft Life-Sciences Alliance, the IME interacts with other Fraunhofer institutes as well as national and international research organizations, universities and partners in industry. This allows all collaborating organizations to pool their resources and competencies, providing a network of expertise, services, innovative enabling technologies, scientists and specialists from a wide variety of backgrounds.

Prof. Fischer has more than 20 years' experience in research and project development in Germany and the United States.

**Professor Dr. Rainer Fischer**  
**Senior Executive Director**  
[rainer.fischer@ime.fraunhofer.de](mailto:rainer.fischer@ime.fraunhofer.de)



# Fraunhofer Institut Molekularbiologie und Angewandte Oekologie

Division of Molecular Biology  
Forckenbeckstraße 6  
52074 Aachen  
Germany  
Tel.: +49 (0) 2 41/60 85 - 0  
Fax: +49 (0) 2 41/60 85 - 100 00  
Website: [www.ime.fraunhofer.de](http://www.ime.fraunhofer.de)

## Molecular Biology Division



Quelle: Birgit Kutzera | panthermedia



## Molecular Biology Division

### **Mission:**

**The development and use of innovative solutions and product candidates for the diagnosis and treatment of human and animal disease as well as the protection of crop plants and food sources.**

For over 50 years the IME has facilitated research and development for innovative products and procedures, helping customers and partners in the pharmaceutical, agronomic, food and nutrition industries. The creation of the Molecular Biology and Applied Ecology Division has allowed us to focus our R&D activities in specific areas, allowing us to reduce the product-to-market time for our customers and partners, develop innovative technologies in the field and provide a portfolio of patents and technologies for our customers and collaborators.

Under the leadership of Prof. Dr. Rainer Fischer, the Molecular Biology Division focuses on the following established business areas:

- Functional and Applied Genomics
- Pharmaceutical Product Development
- Integrated Production Platforms
- Plant Biotechnology
- Customer Contract Services

More recently we have also developed two new business areas which will help to broaden and strengthen our core competences and commercial potential:

- White Biotechnology
- Systems Biotechnology





## The Molecular Biology Division Moves into its New Home

After a two-year construction phase made possible through a € 33.3 m grant from the "Bund" and the "Land Nordrhein-Westfalen (NRW)", the Molecular Biology Division proudly presents its new facility in Aachen. The Division's 60 personnel moved from spare facilities at the RWTH Aachen into the new building in December 2005. The new structure includes 5,400 m<sup>2</sup> of office and laboratory space, a 1,000 m<sup>2</sup> greenhouse, level I and level II containment facilities and a 600 m<sup>2</sup> GMP facility containing two multipurpose production lines for pharmaceutical proteins.

The new work space provides an optimal work environment for our employees and collaborators. The building lies close to the RWTH and to two other Fraunhofer institutes, the Institute for Laser Technology (ILT) and the Institute for Production Technology (IPT), promoting further collaboration. The new building boasts a cafeteria, inner courtyard and garden to provide attractive surroundings for meetings and networking.

### Infrastructure

The Molecular Biology Division benefits from an extensive list of state-of-the-art equipment, highlights of which are listed in Box 1.

#### 5 Box 1 – State-of-the-art equipment available in the Molecular Biology Division

■ Automated DNA-isolation station	■ Biomek 2000/Biomek FX robotic stations	■ ABI 3730 DNA-Analyzer
■ ABI PRISM 7700 Sequence Detection System	■ QPix colony picker and micro array system	■ ScanArray 5000 biochip analysis system
■ Fuji phosphor and chemiluminescent imaging system	■ Leica TCS-SP spectral confocal microscope	■ OPERA high-throughput confocal imaging system
■ Fuji LAS 1000 cooled camera system	■ Fuji FLA 2000 bio imaging analysis system	■ Luigs and Neumann microinjection suite
■ Beckton Dickenson FACScalibur	■ Beckton Dickenson FACSvantage	■ Dade Sercent Wash Centrifuge
■ Schäfer Casy Cell Counter	■ Cell culture laboratories	■ Palm microbeam laser microdissection system
■ Particle gun	■ Fermenters for plant, animal and microbial cell cultures	■ Carr P6 Powerfuge
■ Pharmacia Äkta Explorer	■ Pharmacia Process System	■ ELISA Reader
■ SLM Aminco Bowman AB-2 fluorimeter	■ Pharmacia BIAcore 2000	■ Nonius X-ray diffractometer with Mar 345dtb detector and Oxford Cryosystem
■ Nano-HPLC (Dionex) coupled Waters ESI-Q-TOF-2 mass spectrometer	■ CSC nano-DSC and nano-ITC calorimeters	■ BIAcore 2000 and T100 SPR systems
Graphics workstations including stereo devices and software for solving and analyzing protein structures		
Princeton back-illuminated frame-transfer cooled CCD camera system, 2 photometrics cooled CCD cameras and Leica DM		

Advertisement

Since the year of establishment in 1962, we have continuously been designing and implementing laboratories for research and teaching in their respective disciplines in Germany and abroad. One of our main principles is to respect the history and cultural background of the site as well as its ecological and economic conditions.

Since many years we pursue an integrated environmental policy that includes the buildings and the infrastructure. Sustainable building and running is another goal we try to achieve by closely cooperating and fine-tuning with the Client and user.

With the design and implementation of the Fraunhofer Institut for Molecular Biology and Applied Ecology (IME) in Aachen we have been highly successful in meeting our objectives

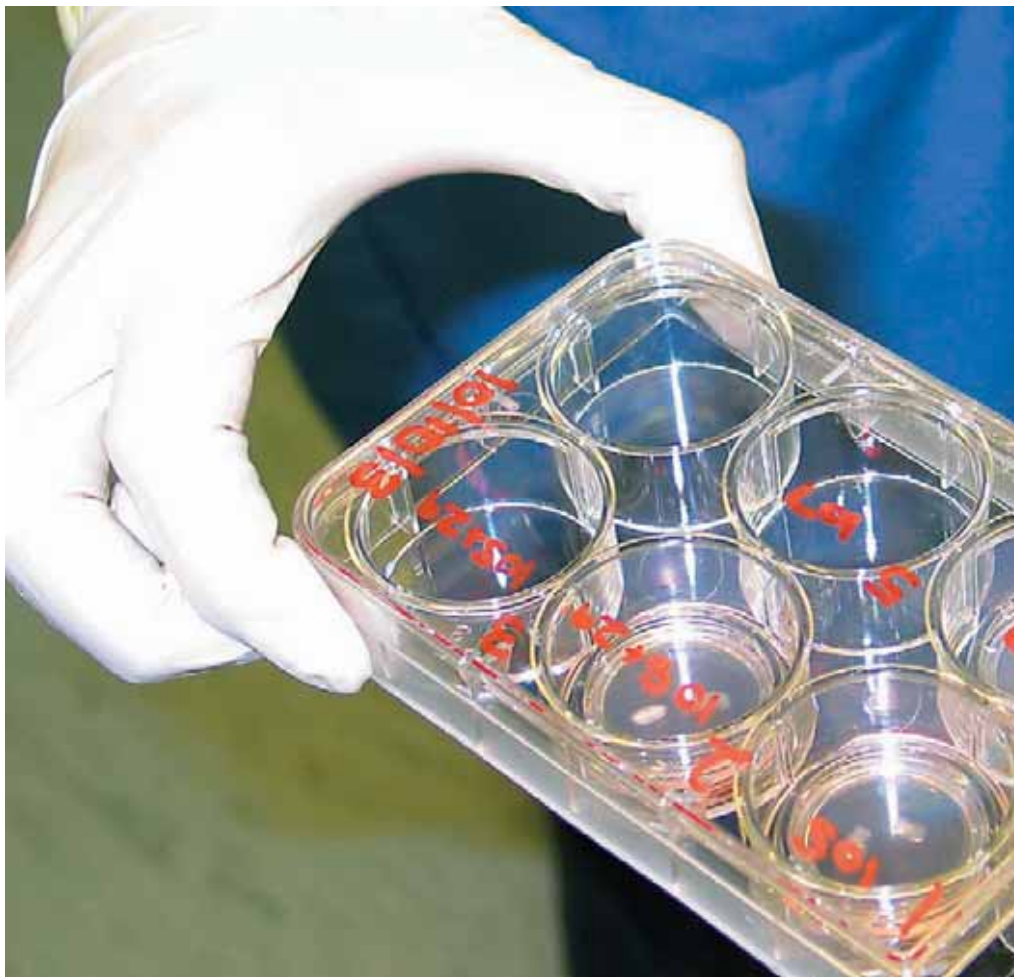
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## Functional and Applied Genomics



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Established Business Areas

## Functional and Applied Genomics

The Functional and Applied Genomics business area focuses on the expression of recombinant proteins in microbial, animal and plant cell cultures. Within this area, novel methods have been developed for increased cell culture productivity, protein expression and cell transformation. The technical developments in Functional and Applied Genomics are used to facilitate the identification and characterization of new substances as well as targets for pharmaceutical product development and plant protection. New target substances are identified from selected organisms through high-throughput analysis (2D gels, chip technologies and combinatorial libraries) and tested in collaboration with group members from other business areas for their effectiveness and safety.

pharmaceuticals and biopolymers with enhanced yields

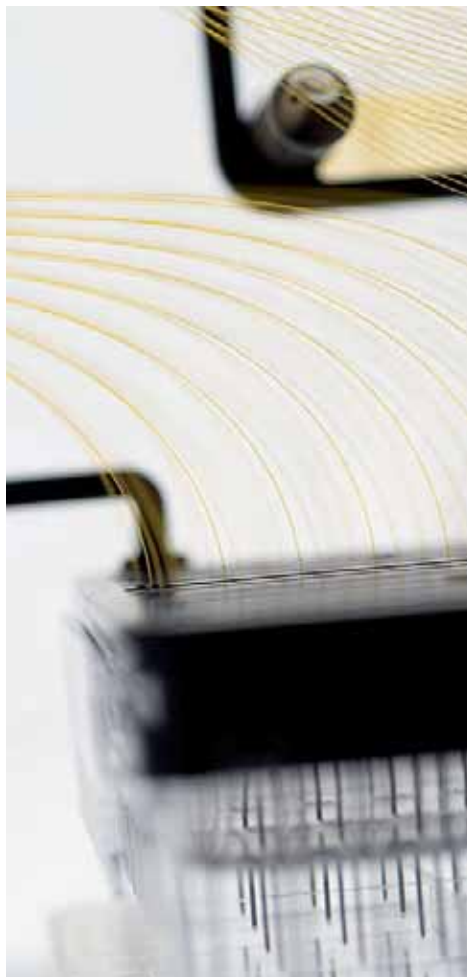
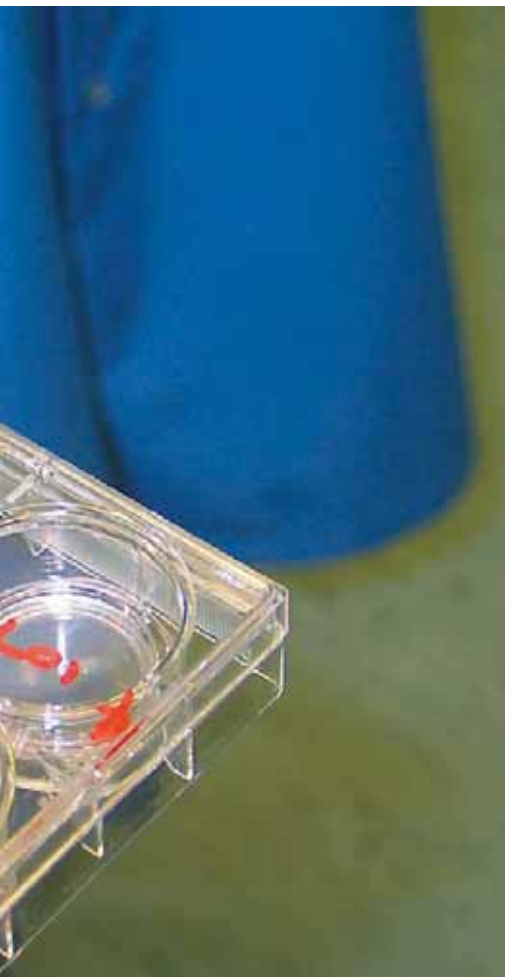
- Optimization of cell cultures
- Novel transformation techniques
- Novel selectable markers from prokaryotes and eukaryotes
- Tilling-based mutagenesis
- Automated systems for high-throughput screening
- Nanobiotechnology

### Major Research and Development Areas

- Identification of novel active substances from medicinal plants
- Production of new targets for drug discovery
- Chip-based identification of valuable structural genes and control elements from prokaryotes and eukaryotes
- Establishment of novel plant-based systems for the production of recombinant

For further information:

Prof. Dr. Dirk Prüfer  
dirk.pruefer@ime.fraunhofer.de



#### Key Achievements

- A new technique for discovering improved genetic control elements from microbes, animals and plants
- The development of different approaches to accelerate the discovery of constitutive and inducible promoters
- The availability of new cell cultures and production lines
- Progress in the development of an alternative system for the stable transformation of single plant cells
- Progress towards engineering the isoprenoid pathway in plants (see Research Highlights 1)
- Progress towards understanding the structure and applications of forisomes
- The development of amylose-free potato varieties without genetic engineering

## PATRIK MÜLLER, GESUNDHEITSPIONIER, PRODUZIERT LEBENSQUALITÄT.

Gemeinsam mit rund 10.000 Mitarbeitern von Roche Diagnostics in Deutschland arbeitet Patrik Müller an Innovationen für die Gesundheit. Der Ingenieur für Biotechnologie ist für die Produktion eines pharmazeutischen Wirkstoffs verantwortlich, mit dem Ärzte Anämien von Menschen mit Nieren- oder Krebserkrankung behandeln können. Dieser Wirkstoff fördert die Bildung roter Blutkörperchen – und verbessert damit deutlich Leistungsfähigkeit und Wohlbefinden der Patienten.

Wir forschen für Ihr Leben gern.



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[www.roche.de](http://www.roche.de)





## Pharmaceutical Product Development



Quelle: MEV-Verlag

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Established Business Areas

## Pharmaceutical Product Development

The Pharmaceutical Product Development business area focuses on the optimization of commercially established or pharmaceutically relevant diagnostic and therapeutic products, particularly monoclonal antibodies and novel products based on antibodies, including antibody fragments and fusions. In the past 25 years such products have been used extensively in medical diagnosis and therapy, although only recently has it been possible to move away from expensive production platforms using mammalian cells towards more cost-effective alternatives.

Novel, disease-specific antibody reagents are isolated from immunized animals by means of proprietary immunization protocols and hybridoma technology, and human recombinant antibodies and antibody fragments are generated using the human B-cell pool. Rational protein design is promoted through combinatorial methods involving molecular evolution, which optimizes these recombinant reagents, and the production of diagnostic and therapeutic products for clinical use is optimized using well established commercial tools. The effectiveness of the molecules is then investigated in various preclinical in vitro and in vivo test systems. Lastly, the new

recombinant proteins are used for a variety of applications: they are developed as diagnostic or therapeutic agents, in particular for clinical applications; they are integrated into in vitro diagnostic systems and kits for the detection of human, animal or plant pathogens; and they are used in the development of protein chips.

### R&D Opportunities:

- Generation of innovation by contract-based research from idea generation over proof of concept to new intellectual property
- Expression, purification, biochemical characterization of any recombinant protein under GLP in systems available (E.coli, yeast, mammalian cells) (GMP available at the department of integrated production platforms)
- Realization of preclinical in vitro analysis and in vivo experiments (subcutaneous, disseminated, orthotopic models)
- Integration of recombinant biology to functionalized planar and nanoparticle surfaces
- Assay development including diagnostic tools based on protein/substrate interaction

For further information:

Prof. Dr. Dr. Stefan Barth  
stefan.barth@ime.fraunhofer.de





#### Major Research and Development Areas:

- Disease indications – cancer, infectious diseases, allergy and autoimmune diseases
- Pathogen detection
- Bioinformatics
- Protein chip technologies
- High-throughput imaging
- Protein expression and purification

#### Key Achievements:

- Development of recombinant immunotherapeutics for the treatment of atopic diseases
- Generation of novel antibodies against adenocarcinoma for molecular imaging (see Research Highlights 2)
- Development of HCV protein chips
- Novel recombinant immunotoxins for the treatment of AML
- Generation of novel immunotherapeutics for the treatment of cancer
- Immunotherapy of obstructive lung diseases using an antibody-based construct

## Forschung für die Medizin der Zukunft

Getragen von bahnbrechenden neuen Erkenntnissen in Genetik, Molekularbiologie und Biochemie verspricht die Molekulare Medizin durch frühzeitige Erkennung sowie durch wirksame personalisierte und zielgerichtete Behandlung von Krankheiten auf molekularer Ebene die Lebensdauer und -qualität von Patienten wesentlich zu verlängern und zu verbessern. Philips hat es sich zum Ziel gesetzt, die wissenschaftliche Forschung durch die Einführung klinisch nutzbarer Lösungen in die Praxis umzusetzen. Diese Herausforderung wird von Philips Research aktiv durch den Programmbereich „Molecular Medicine“ in enger Zusammenarbeit mit industriellen und akademischen Partnern durch Forschung auf den Gebieten der molekularen Bildgebung, der molekularen Diagnostik sowie der molekularen Therapie unterstützt. So hat die Philips Forschung in Aachen seit drei Jahren ein gemeinsames Projekt mit Fraunhofer IME (Abteilung Pharmazeutische Produktentwicklung), in dem zellspezifische Nanomaterialien für die Molekulare Bildgebung erforscht werden. Diese neuartigen Nanomaterialien zeichnen sich durch Kopplung von zellspezifischen rekombinanten Antikörperfragmenten an eine kontrastgebende Einheit wie z.B. hocheffizient lumineszierende Nanopartikel aus. Zudem erforscht der Verbund LUNA seit April 2006 gefördert durch das BMBF und koordiniert durch die Philips Forschung an der frühzeitigen Detektion von Adenocarcinomen mittels optischer Bildgebung. Neben Fraunhofer IME (Prof. Dr. Dr. S. Barth) sind weitere Partner die Universitäten Osnabrück (Prof. Dr. M. Haase), Hamburg (Prof. Dr. H. Weller) und Münster (Prof. Dr. C. Bremer), Bayer BTS (Dr. W. Hoheisel). Die Arbeiten umfassen die Synthese neuartiger lumineszierender Nanopartikel, deren Oberflächenfunktionalisierung sowie die Kopplung an rekombinante anti-MUC-I Antikörper. Die Zellspezifität der Biokonjugate gegenüber Tumorzellen wird sowohl in-vitro als auch in-vivo untersucht werden.

Dr. Helga Hummel  
Philips Technologie GmbH  
Forschungslaboratorien Aachen  
Tel.: 0241-6003-766,  
e-mail: helga.hummel@philips.com



Konfokal-fluoreszenz-mikroskopische Aufnahme einer Zelle markiert mit rot emittierenden Nanopartikel-scFv-Konjugaten

## Integrated Production Platforms



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Established Business Areas

## Integrated Production Platforms

The Integrated Production Platforms business area helps to develop new production processes for industrial partners, taking factors such as the potential market and pharmaceutical applications of the intended product into account. In particular, the business area identifies challenges that may develop in later stages of process engineering or commercialization. It does so during early laboratory-scale process development by examining factors such as the following which affect the performance of the production system: properties of the gene and expression construct; the characteristics of the recombinant protein; downstream processing issues; and regulatory and intellectual property issues which might become relevant in the future.

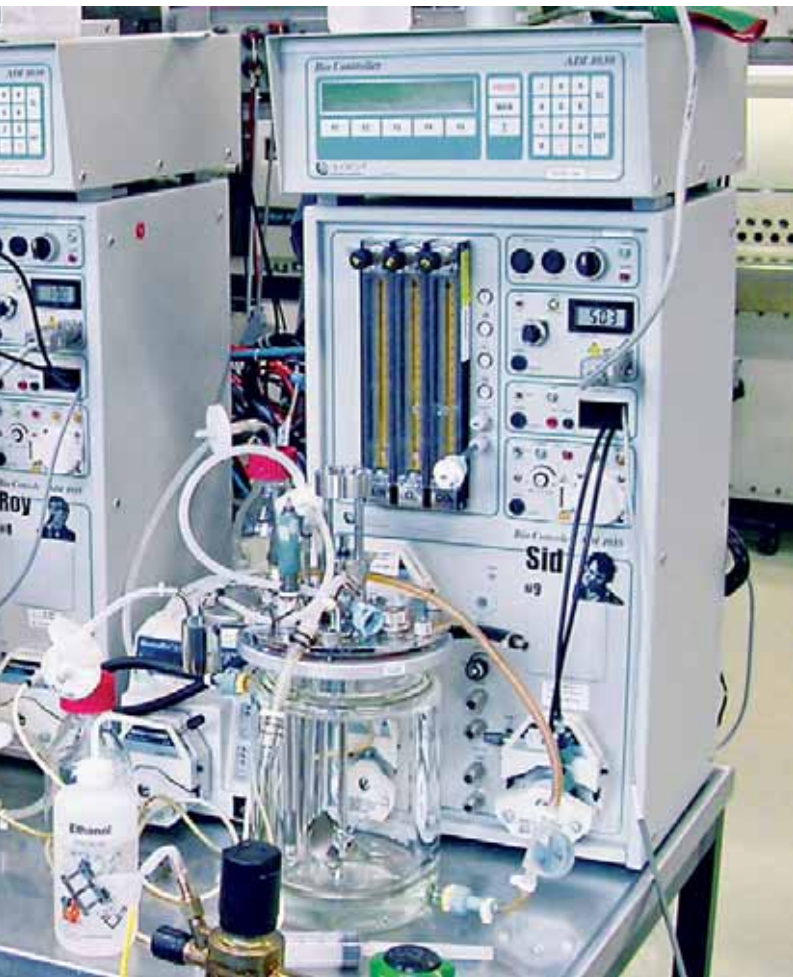
The maintenance of a production suite to supply useful amounts of pure recombinant proteins is too expensive for most research groups in biotechnology. Having produced over 100 different recombinant proteins in bacteria, yeast, plant cell culture, animal cell culture and transgenic plants, the recombinant protein production expertise in the Integrated Production Platforms business area offers a professional and cost-effective solution to these challenges. We offer a certified GMP pilot plant for the production of recombinant proteins under the highest quality standards (see Research Highlights 3).

For further information:

Dr. Jürgen Drossard  
[juergen.drossard@ime.fraunhofer.de](mailto:juergen.drossard@ime.fraunhofer.de)

Dr. Stephan Hellwig  
[stephan.hellwig@ime.fraunhofer.de](mailto:stephan.hellwig@ime.fraunhofer.de)





11

**professional**  
**Riebesam**

Reinigungs-, Desinfektions- und Trocknungsautomaten



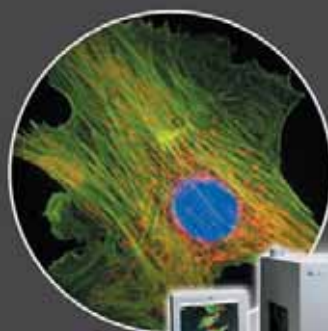
- Professionelles Gerätekonzept „Made in Germany“, zertifiziert nach DIN EN ISO 9001:2000 und DIN EN ISO 13485:2003 (Medizinprodukte).
- Produktpalette vom Untertischgerät bis zum Großkammerautomaten für Labor, Gesundheit, Industrie und Pharma
- Hohe Ausstattungs- und Leistungsvariabilität (z.B. variable Einsätze und Kammergrößen, Final Rinse mit / ohne Zusatztank)
- Desinfektion gemäß §10c BseuchG und DIN EN ISO 15883
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Tel. +49 3933 9332-39 • Fax +49 3933 9332-40  
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## Integrated Production Platforms



Quelle: LSA GmbH | FH-IME

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Established Business Areas

### Major Research and Development Areas:

- Protein production services. We have more than 10 years of experience in contract recombinant protein production.
- Microbial production platforms (bacteria and yeast)
- Mammalian cell production platforms (particularly CHO cells)
- Plant cell cultures. The Integrated Production Platforms business area has 10 years of experience in plant cell cultures and is among the top ten groups globally to use plant cells on an industrial scale.

### Key Achievements:

- Production and purification of over 100 proteins using a variety of different production systems
- Significant expertise in the large-scale production of recombinant proteins in yeast
- We are one of only a few groups to have developed successful cryopreservation protocols for different plant cell lines.

For further information:

Dr. Jürgen Drossard  
[juergen.drossard@ime.fraunhofer.de](mailto:juergen.drossard@ime.fraunhofer.de)

Dr. Stephan Hellwig  
[stephan.hellwig@ime.fraunhofer.de](mailto:stephan.hellwig@ime.fraunhofer.de)



# NewLab BioQuality AG – Solution for the quality control of biopharmaceuticals

NewLab BioQuality AG is an international service provider of quality control analysis for biopharmaceutical drugs. The services offered are in strict compliance to GLP or GMP and satisfy regulatory authorities worldwide.

NewLab BioQuality has continuously expanded its range of services to become a full service supplier for all kinds of quality and safety testing of biopharmaceutical products. The company offers expertise in the areas of protein chemistry, molecular biology and virology.

We assist our clients in all aspects of quality and safety and lead them through the entire process of product development, from the preclinical phase to market approval. Our scientists and skilled technical staff have profound professional commitment in all areas of biotechnology. This is the fundamental base for our success. We see to it that projects are handled with maximum care and the necessary scientific experience.

With more than 10 years of collaboration with both international pharmaceutical companies as well as with smaller biotech companies, NewLab BioQuality AG has a wealth of experience from which it can draw in assisting clients in determining and solving their quality control requirements.



## Contract Services on Biopharmaceuticals



- > Cell line characterization and safety testing
- > Process evaluation for viruses and prions, contaminants and impurities
- > Protein chemistry, product characterization and lot release testing
- > Bioassays
- > Plasmid analysis and DNA sequencing
- > Stability testing on proteins and plasmids



## Plant Biotechnology



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Established Business Areas

## Plant Biotechnology

The Plant Biotechnology business area uses applied biotechnology to modify plants and improve their agronomic traits. This area also focuses on metabolic engineering in plants to increase or reduce the accumulation of specific secondary metabolites. This facilitates the production of valuable plant metabolites and improves the nutritional value of crops.

An important focus within Plant Biotechnology is the improvement of recombinant protein expression and stability in plant cells. We have more than 10 years of experience in the production, characterization and utilization of transgenic plants and are able to provide assistance to customers and collaborators who need transgenic plants that produce novel metabolites or proteins, are resistant to pests and diseases or are engineered for higher nutritional value.

For further information:

Dr. Stefan Schillberg  
[stefan.schillberg@ime.fraunhofer.de](mailto:stefan.schillberg@ime.fraunhofer.de)





Quelle: Bernd Müller

#### Major Research and Development Areas:

- Resistance to viral and fungal pathogens
- Enhanced resistance to insect pests
- Metabolic engineering for enhanced nutritional characteristics in food and feed
- Molecular farming (see Research Highlights 4)

#### Key Achievements:

- The production of antibodies against viral and fungal target proteins and the expression of such antibodies or antibody-fusion protein in plants to provide resistance against viral or fungal diseases
- The development of novel insecticidal toxins through the creation of novel fusion proteins that provide enhanced pest resistance
- The modification of plant metabolism using molecular evolution and protein targeting to optimize enzyme performance and overcome metabolic bottlenecks
- The use of plants and plant cells as factories to produce pharmaceutical proteins and technical reagents in large quantities for industrial customers




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## Customer Contract Services



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Established Business Areas

## Customer Contract Services

In order to promote and encourage research in the different business areas, we have developed various platform technologies that require complex tools and systems in addition to highly trained personnel. These technologies are organized as separate service units within the IME and do not typically belong to specific business areas. The services are available to all working groups at the Institute, as well as external customers on a contractual basis, and include such activities as the purification and crystallisation of proteins, protein structural analysis, high-throughput imaging technologies, mass spectrometry and proteomics, chip technology, DNA sequencing, protein production and antibody manufacturing.

### Key Services

**Protein production.** With the production of several hundred recombinant proteins in a wide range of expression systems over the past 10 years, the IME is a leader in protein production. We have complementary downstream processing equipment as well as numerous stirred-tank bioreactors ranging from 1 to 150 L working volume, ensuring maximum efficiency in process development and the production of non-GMP proteins.

**Antibody technologies.** We provide consultation and contract-based assistance to customers interested in immunization strategies (particularly the immunogenicity and purity of antigens as well as species-related immunological properties), genetic immunization, protein-based immunization, in vitro immunization and the generation of polyclonal, monoclonal and recombinant antibodies.

**Flow cytometry.** We provide our customers with highly skilled specialists who use innovative, cutting-edge flow cytometry instruments to provide services such as particle sorting, device sorting, particle/cell analysis and measurement, apoptosis and cytotoxicity assays, and DNA content analysis. As one of the most progressive technologies in microbiology and molecular biology, flow cytometry or FACS (Fluorescence Activated Cell Sorting) allows the measurement of numerous characteristics at the same time, based upon the specific light scattering and fluorescent characteristics of each cell or particle. Single characterized particles or cells can now be isolated and sorted efficiently using microfluidic control devices.

For further information:

Dr. Jost Muth  
jost.muth@ime.fraunhofer.de





# The Chemical Company

BASF stands for expertise in the area of chemistry.

Without chemistry, there would be no innovations and no sustainable development. Chemistry is and remains one of the key disciplines of the future. BASF is making an important contribution toward successfully shaping the future with innovations from the chemical industry – from new and improved syntheses for basic chemicals, intermediates, vitamins, carotenoids or amino acids to creative and market-oriented improvement of materials such as heat and sound insulation properties; from active substance screening and discovery of new fungicides, herbicides and insecticides to tailor-made solutions through the intelligent design of molecular and supra-molecular structures.

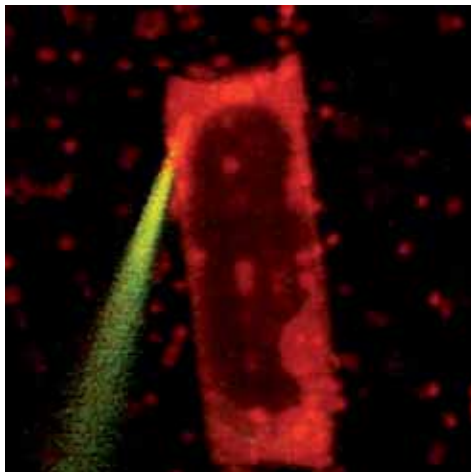


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## Customer Contract Services



### 18 Established Business Areas

**DNA analysis and sequencing.** Our DNA Analysis Facility allows customers easy access to innovative technologies for genome analysis. Recent progress in genome analysis includes improved technology for DNA sequencing, the routine use of DNA microarray technology for the analysis of gene expression profiles at the mRNA level and improved bioinformatic tools to organize and analyse such data. Sequencing is used to characterize new genes and validate the identity of recombinant DNA clones. We assist our customers by offering DNA sequencing and related services such as cloning and plasmid preparation, PCR product purification, preparation of sequencing reactions and sequence analysis. Our sequencing hardware includes an ABI PRISM® 3730 Genetic Analyzer, two ABI PRISM® 310 Genetic Analyzers and two LICOR 4200L DNA Sequencers.

**DNA microarrays.** Our Array Facility carries out the preparation, hybridization and fluorescent quantitation of DNA microarrays, using the Packard Microarray programs Scanarray and Quantarray. In addition, the Array Facility offers researchers the ability to produce their own DNA microarrays.

**Proteomics and protein characterization.** Our Proteomics Facility includes systems for the identification, separation, analysis and quantitation of proteins, the analysis of protein structures and the analysis of protein interac-

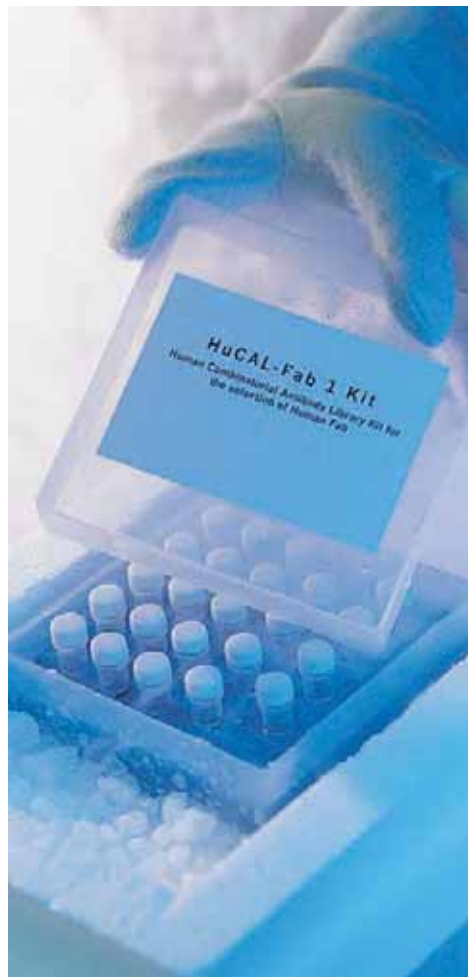
tions. Key resources include the following: two-dimensional gel electrophoresis and multi-dimensional liquid chromatography for protein separation; ESI mass spectrometry (ESI-MS), allowing mass analysis of full-length proteins and protein/ligand complexes; tandem mass spectrometry (MS/MS) for protein identification; and isotope-based methods for semi-quantitative and comparative proteomics. Protein complexes can be analyzed by a combination of affinity purification and MS/MS methods or by surface plasmon resonance using the Biacore systems. Protein stability and binding thermodynamics can be studied by differential scanning calorimetry (DSC) or isothermal titration calorimetry (ITC). The molecular basis of protein function can be studied in a facility fully-equipped for the analysis of each stage, from protein purification and crystallization to X-ray analysis, structure determination and interpretation. The institute has access to a unique system for crystallizing proteins, including in-situ characterization of crystallization droplets using static and dynamic light scattering, as well as modern polarization microscopy technologies.

**High throughput imaging.** Cell-based assays are now part of the cell biology research landscape, and high throughput imaging (HTI) is the technology required to make cell based assays a practical approach for solving problems within the industry, especially in the context of systems biotechnology. We are

For further information:

Dr. Jost Muth  
[jost.muth@ime.fraunhofer.de](mailto:jost.muth@ime.fraunhofer.de)





one of the few research organizations in the world that possesses an Evotec OPERA imaging system which facilitates high-throughput imaging at the single cell level. This provides our customers and partners with a powerful, scarce tool for cell based screening, which can be used for transfection analysis, clone screening, lead identification and assay development (see Research Highlights 5).

**Biorobotics.** We have two multifunctional robotic platforms, a Beckman FX (96-Tip Head) and a Biomek 2000 (8-Tip Head), as well as an automated colony picker to provide support to the DNA Analysis, Array, Proteomics and High-throughput Imaging facilities.

**Bioinformatics.** All our service facilities are supported by our centralized bioinformatics suite. This suite features access to the latest computer programs for data mining, analysis, storage and exchange and access to grid computing across the IME sites to facilitate data exchange with our customers and collaborators. The use of grid computers also allows us to standardize data in our large-scale systems biotechnology programs. In addition to our regular service activities, we provide follow-up services, such as the conversion of all data into editable file formats and data analysis support.

# CRC

ENGINEERING FOR HIGH-TECH-INDUSTRIES

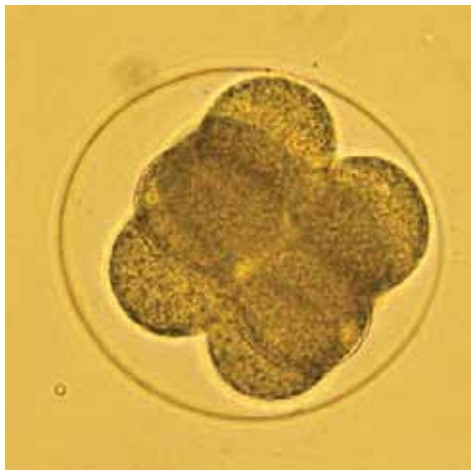


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GESCHÄFTSBEREICHE	KOMPETENZEN	DIENSTLEISTUNGEN	KUNDEN
Life Sciences Mikroelektronik Mikrosystemtechnik	Architektur Technische Gebäudeausrüstung Reine Medien Reinraumtechnik Umwelttechnik Prozesstechnik Qualifizierung und Validierung	Beratung Machbarkeitsstudien Planung Unterstützung bei der Vergabe Bauleitung Facility Management Generalplanung	Fraunhofer Gesellschaft Universitäten GlaxoSmithKline Biologicals Janssen Pharmaceutica Natlmann CAF-DCF (Red Cross Belgium) Schering-Plough Labs Infineon Technologies Robert Bosch GmbH AMI Semiconductor ABB Semiconductors AG

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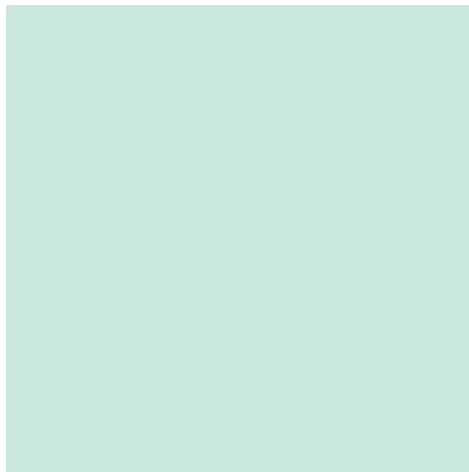
## White Biotechnology



## White Biotechnology

White biotechnology is the new name for industrial biotechnology, i.e. the production of small molecules, polymers and specialty chemicals using living cells. The industrial scale synthesis of small molecules in cells or whole organisms is often more cost effective, efficient and environmentally friendly than established organic chemical processes, especially for the production of complex organic molecules. Furthermore, the use of enzymes or whole organisms producing such enzymes is often the most practical solution for the synthesis of chiral molecules. Embracing white biotechnology as a new business area, we offer a full range of services for the identification, development and production of biocatalysts for use in the bioorganic synthesis of chiral and achiral molecules. In particular, we provide discovery programs, structural analysis and characterization research, molecular evolution for improved catalytic performance and for recombinant enzyme expression using the most suitable platform technology. The emerging White Biotechnology business area is currently linked closely with the established areas of Plant Biotechnology and Integrated Production Platforms.





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## Systems Biotechnology

Systems biotechnology is a new approach for a new millennium. Traditionally, research has focused on single genes and the analysis of individual proteins, with their functions in the context of the whole organism being established through painstaking experiments. The genomics revolution saw a switch from this reductionist approach to a new holistic model in which biological systems are first studied by enumerating their components and then seeing how they all fit together. The increased focus on holistic biology has resulted in the establishment of a new discipline of systems biology. In this new discipline entire biological systems are studied through a combination of high-throughput genomic and post-genomic research in combination with sophisticated and powerful computer modelling, with both the data-driven and modelling components feeding each other with data in iterative cycles to improve the quality and accuracy of the models. We are proud to embrace this new development in biology and are implementing a new initiative within the Institute which will harness the powerful tools of systems biology for the benefit of our customers and collaborators. Through interactions with other Fraunhofer institutes providing modelling expertise and grid computing resources, we will focus our high-throughput genome-scale analytical methods on the discovery of drugs, vaccine

candidates, novel bioactive molecules and the improvement of production platforms. This will involve both empirical experiments and modelling to predict how entire process trains for recombinant proteins perform. We are delighted to be expanding into such an exciting and innovative new area of life sciences research.



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## Research Highlights



### Research Highlights 1 – Exploiting the isoprenoid pathway in plants

One of the research topics addressed in the Functional and Applied Genomics business area is the exploitation of metabolic pathways in plants. For example, many isoprenoids have medically or nutritionally relevant properties and, thus, have a potentially enormous economic impact. We have set out to generate plants with higher yields of economically relevant triterpenoids or novel triterpenoids by expressing known biosynthetic genes from the model plant *Arabidopsis thaliana* in a range of other plant species. In preliminary research, five genes from the pathway were overexpressed in tobacco and *Arabidopsis*, and a rapid thin-layer chromatography procedure was developed to screen the plants for isoprenoid compounds. A novel substance was identified in one plant line, which is now being characterized.

### Research Highlights 2 – Producing novel imaging reagents

Successful molecular imaging requires a strong signal, high resolution, and most importantly, specificity. A multidisciplinary team of researchers has joined the Pharmaceutical Product Development business area to develop a new family of targeted contrast agents for use in molecular medicine by conjugating recombinant antibodies to quantum dots. The aim

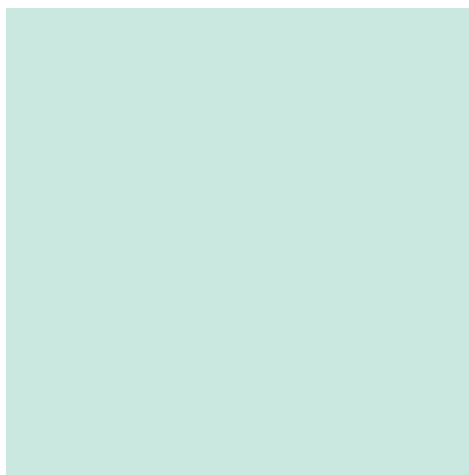
is to develop targeted contrast agents applicable in oncology, cardiovascular disease and chronic inflammation. We have succeeded in joining two molecules in an oriented and covalent fashion to provide maximum access to the antigen binding site. The constructs were stable in human serum for several weeks. Using confocal microscopy, we were able to demonstrate specific binding to cell lines expressing the appropriate antigen, whereas there was no binding to non-expressing cell lines. We have now conjugated a range of antibodies to quantum dots, demonstrating the universal applicability of our linking technique.

### Research Highlights 3 – Our new GMP facility

Measures to harmonize European and worldwide regulatory guidelines have led to an increased demand for protein production according to good manufacturing practice (GMP). For products developed by research groups that are not able to invest in their own GMP pilot plant, finding capacity and funding to move drug candidates toward clinical trials is a significant challenge.

In order to allow the Integrated Production Platforms business area to extend its contract manufacturing services to such groups, a multi-purpose GMP-compliant pilot production plant has been constructed as part of ►





## DER EIGENE WEG

**GRÜNENTHAL** is an independent, research-based, pharmaceutical company operating internationally. Future consolidation by means of innovative research is an integral part of our company policy. Grünenthal's ambition is to be a leading R&D company in selected indications: pain is our core competence.

## Research Highlights



... the new IME building in Aachen. The facility covers 600m<sup>2</sup> and comprises two independent multi-purpose GMP production lines with completely separated rooms and HVAC systems for the production of recombinant biopharmaceutical APIs. A 15-100-350 L fermentation train and matching downstream processing equipment can be found in each line. In addition, rooms for in-process control, cell banking, media preparation, cleaning and storage of equipment are provided.

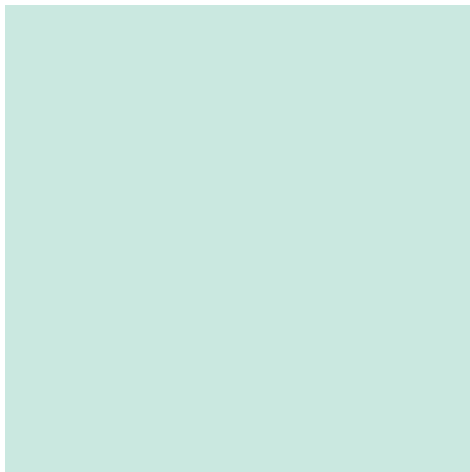
We offer these services to diverse customers: small biotechnology companies wishing to move their products towards commercialization while maintaining their own independence; contract research organizations seeking additional capacity; and large pharmaceutical companies needing to reduce their product-to-market time and outsource labour-intensive tasks such as strain and process development.

### Research Highlights 4 – Molecular Farming and the Pharma-Planta Consortium

The diagnosis and treatment of many diseases will become more efficient in the future as more protein reagents and pharmaceuticals become available. However, as the demand for such molecules increases, our traditional microbial and mammalian cell systems for

large-scale production will be less able to provide the necessary capacity. Molecular farming, which involves the production of recombinant proteins in plants, is an alternative approach currently being explored by the Plant Biotechnology business area. Many plant-derived pharmaceutical proteins have been produced successfully, including antibodies, blood substitutes, vaccines and enzymes. Molecular farming has a number of advantages over conventional processes, since plants can produce functional proteins on a large scale with relatively little cost and effort. The production of recombinant proteins requires intact plants, which are cultivated in the open field or greenhouse, or plant cell cultures, which are cultivated under controlled conditions in bioreactors. The IME has extensive expertise in both areas, which is further encouraged and developed through teamwork with our international partners. One example is the Pharma-Planta program, a five-year collaborative integrated research project funded under EU Framework 6. The aim of the project is to move plant-made pharmaceuticals beyond proof-of-concept and develop candidate plant-derived products for clinical evaluation in phase 1 human trials.





# HPC



## High Performance Computing



High Performance Computing (HPC) projects, which are distinguished by their high level of complexity, run in many public facilities for research and teaching.

In order to deliver such projects via partners, HP has set up the "High Performance EMEA Partner Program" (HEPP). The first – and so far the only – partner to qualify for the programme is Bechtle AG. The most important aim of the co-operation between HP and Bechtle is the best possible supervision of research facilities thanks to top product know-how and reliable service.

Bechtle has established six purpose-built performance centres in selected system houses, one of which is the Bechtle GmbH in Munich. There you will find experienced specialists with the necessary know-how for supervising technically demanding computer centres in universities and research institutes.

We look forward to hearing from you!

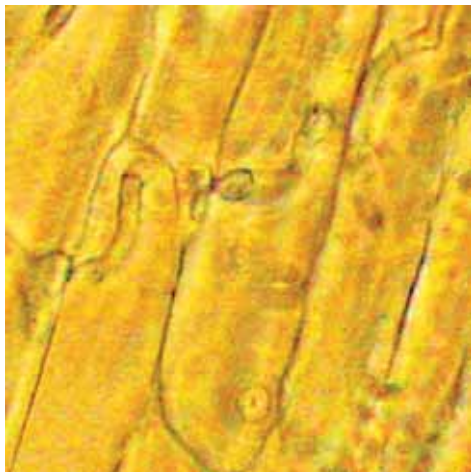
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## Research Highlights



### Research Highlights 5 – Opera automated high-throughput confocal microscopy

The Opera microscope is a fully automated confocal imaging system that combines the power of quantitative fluorescence with the subcellular resolution of confocal microscopy. The system is based on dual Nipkow spinning disk confocal technology and is equipped with four excitation lasers (405, 488, 561, 635 nm) coupled to three independent CCD cameras for multiplexed analysis of up to four measurable parameters. The system is compatible with all running plate formats (from 96 to 2080-well plates), allowing for high speed and high density data acquisition and analysis.

The IME is one of the few research organizations in the world to own an Opera system equipped with an environmental control unit, which makes the analysis of cellular processes under controlled growth conditions possible. This provides both reproducibility and flexibility in complex, large-scale experiments.

The Opera system is coupled with software for automated image analysis. This extracts large image-based datasets and converts the images into quantitative data, enabling the system to be used for assay development and sophisticated screening. Our portfolio includes

assays for the analysis of transcriptional activation, endocytosis and GPCR trafficking. We also provide small scale screens of custom compound and siRNA libraries for pathway dissection and target identification. The system is well suited to clonal selection and the quantitative analysis of fluorescent fusion protein expression under multiple growth conditions. The large image datasets generated using the Opera system are ideal for model development and validation, allowing for unprecedented in silico analysis and the optimization of industrial biotechnology processes.





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## The Fraunhofer Center for Molecular Biotechnology



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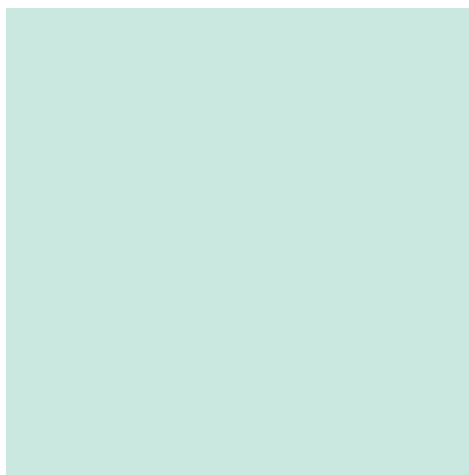
The Fraunhofer Center for Molecular Biotechnology

## The Fraunhofer Center for Molecular Biotechnology

The Fraunhofer USA Center for Molecular Biotechnology (CMB) focuses on the development of platform technologies and novel products in the field of vaccine research. The Center has 50 full-time employees, as well as two visiting graduate students and two part-time personnel. Key recent developments at the CMB include the fusion of target vaccine peptides to the coat protein of the alfalfa mosaic virus for enhanced presentation to the immune system and the fusion of vaccine peptides to *Clostridium thermocellum* lichenase to improve target stability and recovery. The CMB has also developed its proprietary 'Launch Vector' technology, which integrates gene transfer to plants using *Agrobacterium tumefaciens* and expression using viral vectors. The 'Launch Vector' system significantly reduces the production time for recombinant proteins, thus facilitating a rapid response to emerging pandemic diseases such as avian influenza. In addition, the CMB has created a new technology for the contained production of recombinant proteins. This technology is based on clonal cell cultures in which a plant virus containing a particular transgene replicates and produces the recombinant protein.

The success of the CMB's core R&D activities has attracted significant funding, including \$10 m in basic funds from the Fraunhofer-Gesellschaft, \$5 m in basic funds from the State of Delaware and more than \$6 m from the Bill and Melinda Gates Foundation for three independent projects designed to help develop vaccines against malaria, trypanosomiasis and pandemic strains of avian influenza. Two of these projects, a \$2.7 m grant to help create a vaccine against pandemic strains of avian influenza and a \$3.5 m grant to help invent a transmission-blocking vaccine against malaria, were initiated in 2006.





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