Fraunhofer
IZI

FRAUNHOFER INSTITUTE FOR CELL THERAPY AND IMMUNOLOGY IZI

ANNUAL REPORT 2020
SHORT VERSION

This is the abridged version of the Fraunhofer IZI Annual Report 2020.

The full version can be found at www.izi.fraunhofer.de/en/publications

The report includes a detailed description of selected projects and a list of this year's publications.

Scan the QR codes to go straight to the relevant sections of the annual report.
We recommend that you use the Mozilla Firefox browser for an optimal page display.

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STRUCTURES & FIGURES 2020

PORTRAIT OF THE INSTITUTE

The Fraunhofer Institute for Cell Therapy and Immunology IZI investigates and develops solutions to specific problems at the interfaces of medicine, life sciences and engineering. One of the institute's main tasks is to conduct contract research for companies, hospitals, diagnostic laboratories and research institutes operating in the field of biotechnology, pharmaceuticals and medical engineering.

The Fraunhofer IZI develops, optimizes and validates methods, materials and products within the business fields cell and gene therapy, drugs and vaccines, molecular diagnostics and immunodiagnostics, as well as extracorporeal therapies. Its areas of competence lie in cell biology, immunology, drug biochemistry, bioanalytics and bioproduction as well as process development and automation. Research in these areas is centered around developments in immuno-oncology and infectious disease pathology. The S3 safety laboratory allows research and development activities to be conducted and highly pathogenic agents investigated under biosafety level 3 conditions.

The institute works in close cooperation with hospital institutions and performs quality tests besides manufacturing investigational medicinal products in line with GMP requirements. Furthermore, it supports partners in developing processes for the pharmaceutical production of ATMPs and biologicals, for example by helping them to obtain manufacturing licenses.

ORGANIZATION

DIRECTOR

Prof. Dr. Dr. Ulrike Köhl | PD Dr. Sebastian Ulbert (deputy)

ADMINISTRATION

Anja Bochmann-Seidel | Annette Schäfer (deputy)

EXECUTIVE DEPARTMENTS

- Business Development and Patent Management
  Dr. Thomas Tradler
- Press and Public Affairs
  Jens Augustin
- Occupational Safety
  Dr. Peter Ruschpler
- IT Management
  Alexander Dossin

CENTRAL FACILITIES

- Center for Experimental Medicine
  Dr. Franziska Lange
- Imaging and image analysis
  Prof. Dr. Ulf-Dietrich Braumann
- GLP test facility
  Dr. Jörg Lehmann

OFFICERS

MAIN DEPARTMENT OF GMP CELL AND GENE THERAPY

Dr. Gerno Schmiedeknecht | Kati Kebbel

DEPARTMENT OF GMP PROCESS DEVELOPMENT / ATMP DESIGN

PD Dr. Stephan Fricke

DEPARTMENT OF PRECLINICAL DEVELOPMENT AND VALIDATION

Dr. Jörg Lehmann

- Preclinical Models,
  Sina Riemschneider
- Protein Biomarker,
  Prof. Dr. Stefan Kalkhof
- Cell Line Development,
  Dr. Elke Ueberham
- Veterinary Pathology,
  Dr. Anke Hoffmann

DEPARTMENT OF VACCINES AND INFECTION MODELS

PD Dr. Sebastian Ulbert | PD Dr. Thomas Grunwald

- Vaccine Technologies,
  Dr. Jasmin Fertey
- Preclinical Validation,
  PD Dr. Thomas Grunwald
- Vector-based Immuno-therapy, Prof. Dr. Hildegard Büning | Prof. Dr. Ulrich Hacker
- Infection Models and Immunodiagnostics,
  Dr. Franziska Lange
- Antimicrobial Agents,
  Dr. Andreas Schubert
- Biological Material Analytics (Fraunhofer IKTS ATTRACT-Group), Dr. Juliane Spohn

DEPARTMENT OF DIAGNOSTICS

Dr. Dirk Kuhlmeier

- CardiOmics, Prof. Dr. Dr. Dr. Andreas Oberbach
- Ligand Development,
  Dr. Michael Szardenings
- Experimental Imaging,
  Dr. Sebastian Greiser
- Image Analysis of Cell Function, Prof. Dr. Ulf-Dietrich Braumann
- MicroDiagnostics,
  Dr. Dirk Kuhlmeier
- DNA Nanodevices,
  Dr. David M. Smith
- Next-Generation Diagnostics,
  Dr. Conny Blumert
- Bioinformatics,
  Dr. Kristin Reiche

HEADQUARTER LEIPZIG

April 2021

DIRECTOR BRANCH BIOANALYTICS AND BIOPROCESSES

Dr. Eva Ehrentreich-Förster (temp.)

ADMINISTRATION

Katja Okulla

EXECUTIVE DEPARTMENT

- Marketing & Communication
  Dr. Katharina Kasack

CENTRAL FACILITY

- Extremophile Research and Biobank CCCryo
  Dr. Thomas Leya

OFFICERS

DEPARTMENT OF EXTRACORPOREAL THERAPY SYSTEMS

Prof. Dr. Steffen Mitzner

DEPARTMENT OF DRUG DESIGN AND TARGET VALIDATION

Prof. Dr. Stephan Schilling

- Molecular Biotechnology, Dr. Holger Cynis
- Protein and Drug Biochemistry, Prof. Dr. Stephan Schilling
- Drug Design and Analytical Chemistry, Prof. Dr. Stephan Schilling (temp.)
- Protein Misfolding Diseases, Dr. Anja Schulze
- Astacin Proteases, Dr. Daniel Ramsbeck

DEPARTMENT OF BIOSYSTEM INTEGRATION AND PROCESS AUTOMATION

PD Dr. Ralph Hölzel (temp.)

- ivD Platform / PoC Technologies, Dr. Harald Peter
- Biomolecular Nanostructures and Measurement, PD Dr. Ralph Hölzel
- Biomimetic Functional Materials, Dr. Nenad Gajovic-Eichelmann
- Laboratory and Process Automation, Jörg Henkel

DEPARTMENT OF MOLECULARE AND CELLULAR BIOANALYTICS

Dr. Eva Ehrentreich-Förster

- Microarray and Sensor Technology, Dr. Eva Ehrentreich-Förster
- Biomarker Validation and Assay Development, PD Dr. Harald Seitz
- Molecular Bio Engineering, Dr. Markus von Nickisch-Rosenegk
- Mcrosystems for In Vitro Cell Models, Dr. Katja Uhlig
- Microfluidic Cell Processing and Cell Analytics, Dr. Michael Kirschbaum

DEPARTMENT OF CELL-FREE AND CELL-BASED BIOPRODUCTION

Dr. Stefan Kubick

- Cell-free Protein Synthesis, Dr. Stefan Kubick
- Eukaryotic Lysates, Doreen Wüstenhagen
- Functional Nucleic Acids – Aptamers, Dr. Marcus Menger

ROSTOCK | HALLE (SAALE) | POTSDAM-GOLM

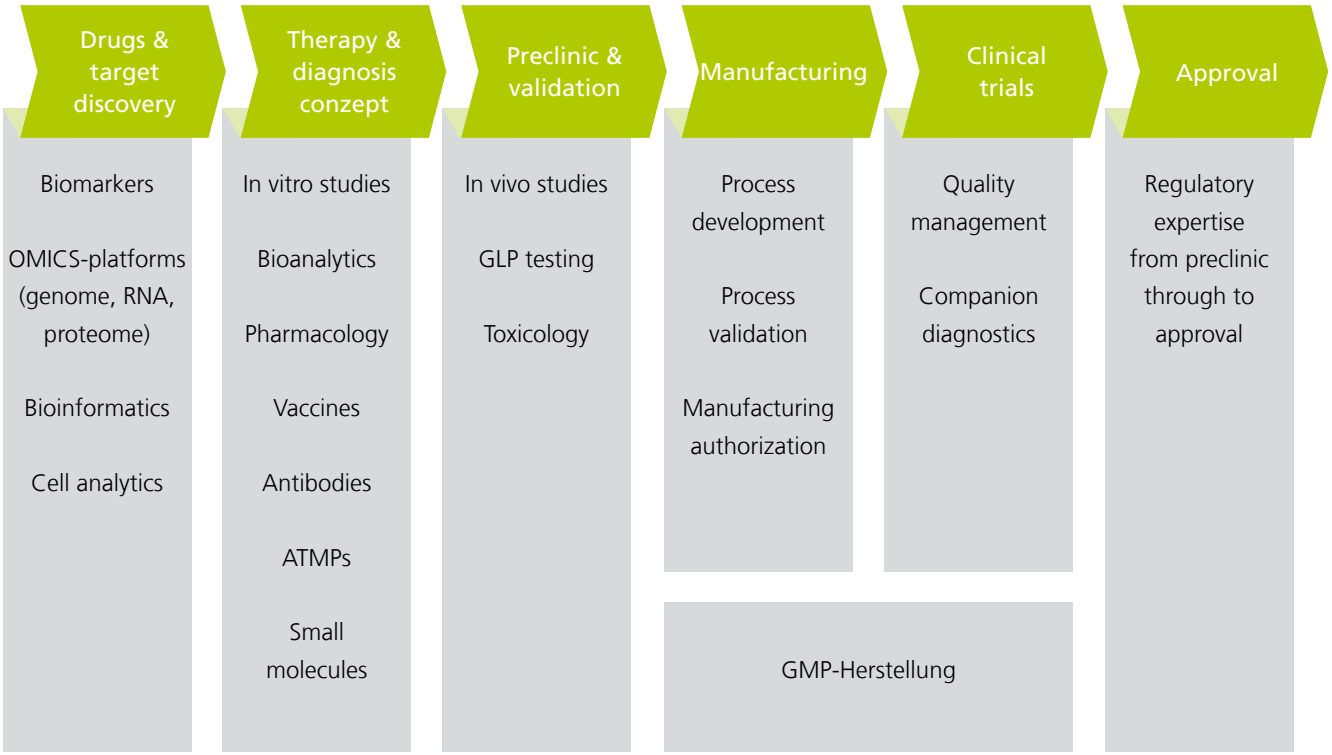
BUNINESS UNITS AND COMPETENCIES

CELL AND GENE THERAPY

DRUGS AND VACCINES

MOLECULAR AND IMMUNODIAGNOSTICS

EXTRACORPOREAL THERAPIES



THERAPEUTIC MOLECULES

CELL TECHNIQUES

BIOANALYTICS

BIOMARKER

SCIENTIFIC PRESENCE AND NETWORK 2020

64 Conventions and conferences

179 Industry partners
172 Research partners

49 Abstracts
77 Publications
1 Book article

46 Teaching activities

1 Habilitation
1 Doctorates
3 Diploma theses
18 Master theses
16 Bachelor theses

50 Patent families
174 Patents and patent applications

55 Evaluator activities

115 Association memberships in various expert associations

Detailed information on key figures and publications can be found in the full version of the annual report on pages 96–135.
https://s.fhg.de/B2E

KEY INSTITUTE FIGURES 2020

EMPLOYEES

by location

30 Rostock

57 Halle (Saale)

107 Potsdam-Golm

453 Leipzig

EMPLOYEES

workforce composition

5 % Trainees / interns / diploma students / bachelor students / master students

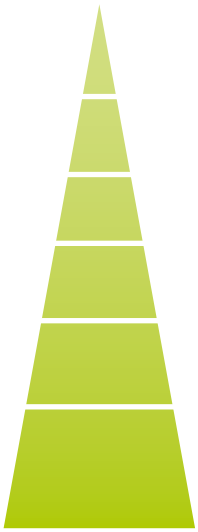
8 % PhD students

10 % Student / scientific assistants

11 % Administration / executive departments / IT / technical infrastructure

19 % Technical assistants and laboratory technicians

47 % Research and technical engineering staff incl. guest researchers



37,9 MIO € PROJECT REVENUE

by location € mio

27,49 Leipzig

6,92 Potsdam-Golm

2,96 Halle (Saale)

0,56 Rostock

PROJECT REVENUE

by funding agency

0,9 % EU (358 TEUR)

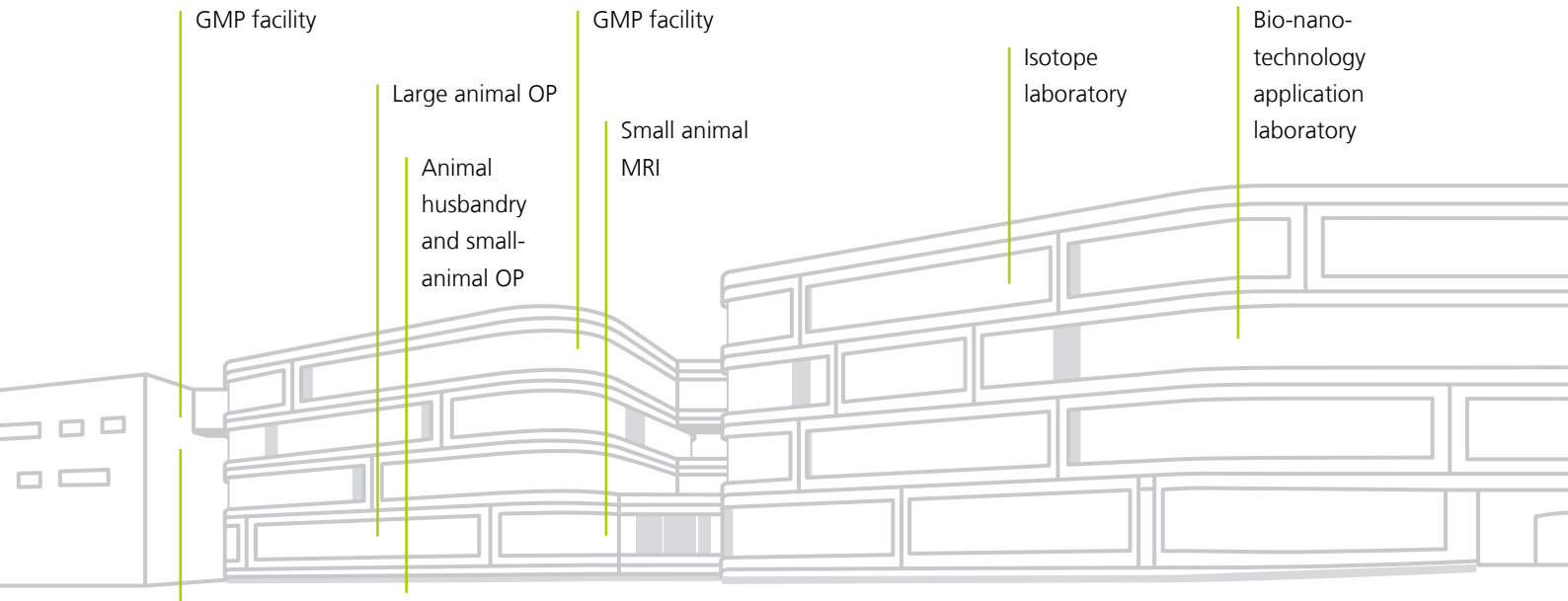
22,2 % Other (8 406 TEUR)

28,6 % German national and regional government (10 850 TEUR)

48,3 % Industry (18 315 TEUR)

December 31, 2020

RESEARCH INFRASTRUCTURE AT THE LEIPZIG SITE



FIRST EXTENSION BUILDING

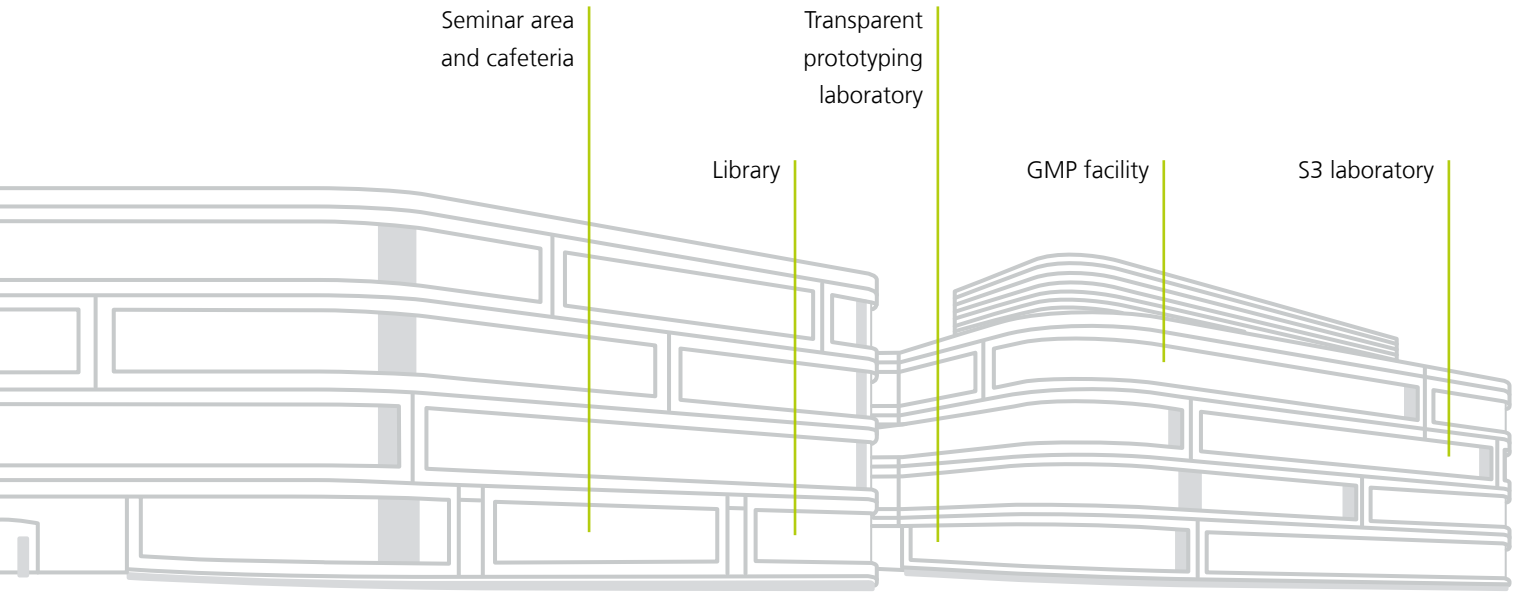
Start-up operations: 2012
Usable area: 1 568 m²
Lab space: 470 m²
Offices: 142 m²
Clean rooms: 410 m²

MAIN BUILDING

Start-up operations: 2008
Usable area: 4 131 m²
Lab space: 1 867 m²
Offices: 1 615 m²
Seminar area: 276 m²

RENTAL AREA AT BIO CITY LEIPZIG

Start-up operations: 2006
Clean rooms: 334 m²



SECOND EXTENSION BUILDING

Start-up operations: 2015
Usable area: 3 050 m²
Lab space: 1 171 m²
Offices: 881 m²
Clean rooms: 402 m²

LOCATIONS & DEPARTMENTS

LEIPZIG, SAXONY, GERMANY

HEADQUARTER

The main building boasts extensive laboratory capacities for conducting molecular and cell-biological work. An extensive immunohistochemistry laboratory, an isotope laboratory, a quality control laboratory with qualified equipment, as well as cyro-storage capacities also make up the institute's facilities.

The research infrastructure at the headquarters is complemented by various special facilities found in the extension buildings (e.g. imaging units, laboratories for experimental medicine, a S3 laboratory, and clean-room facilities).

All of the Fraunhofer IZI's laboratories are certified according to S2 standards and therefore suitable for carrying out work in the fields of genetic engineering and infection biology. A flexible cluster structure allows laboratory sections to be adapted and fitted out in line with the specific requirements of a broad range of projects.

The business units Cell and Gene Therapy, Drugs and Diagnostics are primarily based in Leipzig. Biopharmaceutical products for clinical trials are manufactured in line with Good Manufacturing Practice (GMP) in the institute's clean-room facilities, which cover a total area of 1 200 m².

MANAGEMENT

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LEIPZIG, SAXONY, GERMANY

MAIN DEPARTMENT OF GMP CELL AND GENE THERAPY

The Main Department of GMP Cell and Gene Therapy operates Fraunhofer IZI's three modern GMP facilities consisting of ten separate clean room suites (altogether 21 clean room grade B manufacturing rooms) which have been specially optimized for manufacturing of cell and gene therapy products, so called Advanced Therapy Medicinal Products – ATMP. The particular specialty of the about 130 highly qualified staff members is the GMP-compliant manufacturing and quality control of investigational medicinal products.

GMP-compliant process and quality control development as well as the creation of Standard Operating Procedures (SOPs) are intensively discussed with the project partner before being implemented. The leading staff in charge has many years of experience in designing GMP-processes in the cell and gene therapy area.

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Further information on the department can be found in the full version of the annual report on page 12.
https://s.fhg.de/l64Y

LEIPZIG, SAXONY, GERMANY

DEPARTMENT OF GMP PROCESS DEVELOPMENT / ATMP DESIGN

The Department of GMP Process Development / ATMP Design is responsible for transferring manufacturing processes from the lab into a clinical setting. In order to obtain official manufacturing licenses for the production of clinical test samples, either GMP-compliant processes are developed from scratch or existing processes adapted and optimized.

The department focuses primarily on cell- and gene-based drugs, known as Advanced Therapy Medicinal Products (ATMPs). These include antigen-specific T cells, CAR-T cells, CAR-NK cells, dendritic cells, mesenchymal stem cells (MSC), induced pluripotent stem cells (iPS) and tissue engineering products.

Furthermore, upstream and downstream processes are being developed for biomolecules in single-use reactors with a volume of up to 200 liters.

The development of GMP-compliant manufacturing protocols is closely associated here with the definition of respective quality controls.

In the development unit, process adjustments can be tested and optimized flexibly and cost-efficiently. The impact of new devices, media, seed densities and freezing protocols on the GMP process is also investigated here.

This then enables new processes to be implemented and validated in the institute's GMP clean rooms.

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Further information on the department can be found in the full version of the annual report on page 13.
https://s.fhg.de/t28

LEIPZIG, SAXONY, GERMANY

DEPARTMENT OF PRECLINICAL DEVELOPMENT AND VALIDATION

The main goal of the Department of Preclinical Development and Validation is the concentration of expertise for the preclinical validation of novel therapeutic approaches at IZI, to maximize the efficiency in developing new in vitro or in vivo models and their application in preclinical studies. Since the department manages the GLP test facility of Fraunhofer IZI, all preclinical studies (even those in other Fraunhofer IZI departments) can be performed under GLP.

THE DEPARTMENT COVERS THE FOLLOWING TOPICS

- Planning and execution of preclinical efficacy and safety studies for new drug candidates (especially ATMPs) and medical devices (ISO 10993) under GLP or GLP-analogous conditions. This includes the development and validation of suitable in vitro and in vivo models.
- Developing procedures for the diagnostic analysis of secretory and cellular protein biomarkers, including the development and production of specific monoclonal antibodies for their detection and finally the development and validation of the respective diagnostic assays (e.g. ELISA, lateral flow assays, Luminex®, flow cytometry).
- Identifying and validating new protein biomarkers for diagnosis and therapy of chronic-inflammatory and tumor diseases, as well as for the sector of veterinary medicine / farm animal husbandry.
- Developing human monoclonal antibodies to be directed against new therapeutic tumor targets (triple-negative breast cancer) and to be used as passive vaccines against pathogenic viruses (SARS-CoV-2) besides their further development as drug candidates.

UNITS

- Preclinical Models, Sina Riemschneider
- Protein Biomarker, Prof. Dr. Stefan Kalkhof
- Cell Line Development, Dr. Elke Ueberham
- Veterinary Pathology, Dr. Anke Hoffmann

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Further information on the department can be found in the full version of the annual report on pages 14–16.
https://s.fhg.de/9xC

LEIPZIG, SAXONY, GERMANY

DEPARTMENT OF VACCINES AND INFECTION MODELS

Procedures to stimulate or suppress the immune system are developed in the Department of Vaccines and Infection Models. These include vaccines on innovative technology platforms, e.g. novel inactivation methods or plasmid DNA. As such, efficient vaccines can be produced quickly and inexpensively. An S3 laboratory facilitates work with highly infectious pathogens. In-vivo and in-vitro model systems are also generated and used to develop diagnostic and therapeutic agents.

UNITS

- Vaccine Technologies, Dr. Jasmin Fertey
- Preclinical Validation, PD Dr. Thomas Grunwald
- Inflammation Models and Immunodiagnostics, Dr. Franziska Lange
- Antimicrobial Agents, Dr. Andreas Schubert
- Biological Material Analytics, Dr. Juliane Spohn

CONTACT

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PD Dr. Thomas Grunwald
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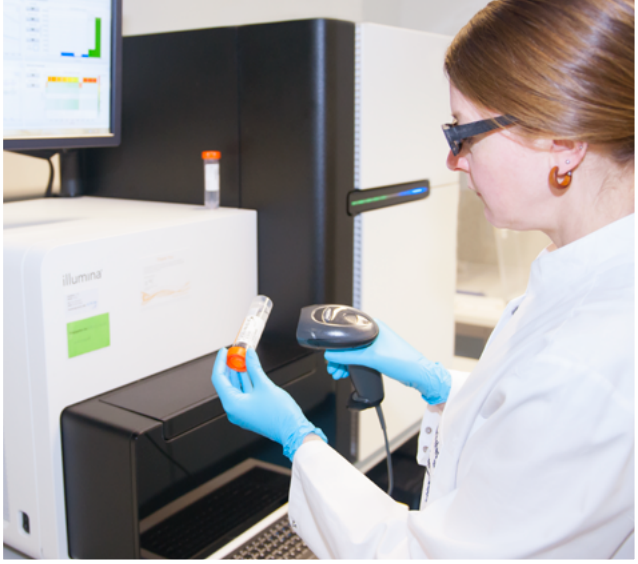
Further information on the department can be found in the full version of the annual report on pages 17–20.
https://s.fhg.de/rk5

LEIPZIG, SAXONY, GERMANY

DEPARTMENT OF DIAGNOSTICS



The Department of Diagnostics offers a value chain that covers the identification and testing of new biomarkers, the bioinformatic analysis of complex transcriptomic and genomic data ("Big Data") as well as the development of prototypes for in vitro diagnostics and point-of-care platforms. Furthermore, it offers a broad range of analytical methods.

In the department's RIBOLUTION Biomarker Center new biomarkers are being systematically identified and validated using state-of-the-art techniques such as next-generation sequencing (NGS) and microarray analysis. A particular focus is on non-coding RNAs, which show high, so far mostly underestimated, biomarker potential. An experienced bioinformatics group provides efficient processing and (statistical) analysis of molecular biological data, particularly of NGS data obtained from large clinical cohorts. Competencies in study and data management enable our scientists to plan and conduct such cohorts. A quality management system has been implemented and certified according to ISO 9001:2015 with an eye to these processes.

A main focus of the department is to develop molecular and immunodiagnostic tests in the medical and food sector. This includes PCR and NGS analyses, lab-on-a-chip systems as well as peptide selection and epitope mapping technologies. Diagnostic needs are addressed e.g. for cancer, cardiological diseases and food allergies as well as pathogen tests for infectious diseases. Moreover, the department has a wide range of additional analytical methods at its disposal and develops novel biointeractive molecules on structural DNA-based scaffolds. New imaging procedures support the analysis of cell biological processes.

UNITS

- CardiOmics, Prof. Dr. Dr. Dr. Andreas Oberbach
- Ligand Development, Dr. Michael Szardenings
- Experimental Imaging, Dr. Sebastian Greiser
- Image Analysis of Cell Function, Prof. Dr. Ulf-Dietrich Braumann
- MicroDiagnostics, Dr. Dirk Kuhlmeier
- DNA Nanodevices, Dr. David M. Smith
- Next-Generation Diagnostics, Dr. Conny Blumert
- Bioinformatics, Dr. Kristin Reiche

CONTACT

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Further information on the department can be found in the full version of the annual report on pages 21–26.
https://s.fhg.de/925

ROSTOCK, MECKLENBURG-WESTERN POMERANIA, GERMANY

DEPARTMENT OF EXTRACORPOREAL THERAPY SYSTEMS

The Department of Extracorporeal Therapy Systems focuses on the development and evaluation of extracorporeal (outside the body), organsupporting technologies with a particular emphasis on supporting the immune system. It offers the full range of preclinical and clinical analyses of extracorporeal technologies based on a broad spectrum of in vitro simulations, animal models, as well as a powerful clinical study network for in and out-patients. Moreover, the department offers self-developed unique analytic and diagnostic devices including an ex situ intestinal model, a cell sensor and novel protein assays.

CONTACT

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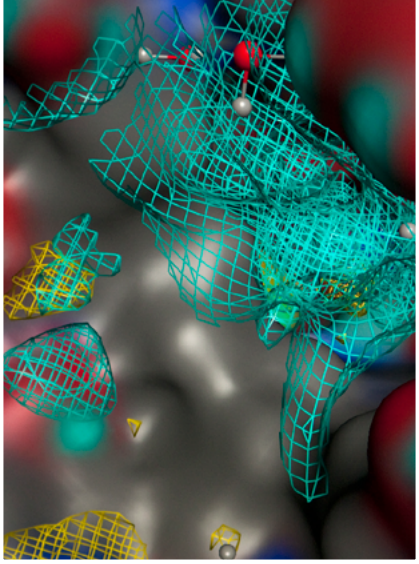
Further information on the department can be found in the full version of the annual report on page 27.
https://s.fhg.de/ANk

HALLE (SAALE), SAXONY-ANHALT, GERMANY

DEPARTMENT OF DRUG DESIGN AND TARGET VALIDATION



The Department of Drug Design and Target Validation in Halle (Saale) boasts considerable expertise in various areas of preclinical drug development, placing a special focus on neurodegenerative and inflammatory diseases. The department's work covers almost the entire range of activities associated with the early stages of drug development, from identifying and characterizing target proteins to identifying initial drug candidates right over to testing substances in the animal model. Members of staff at the Halle (Saale) branch are characterized by their extensive experience in industrial and pharma-relevant research. This allows scientific issues to be tackled on behalf of industry partners on the one hand, and new drugs and target proteins from the institute's own preliminary research to be identified, patented and subsequently form the basis of industry cooperations on the other.

Small molecules and biologicals will be developed and tested on the back of the department's new treatment concepts. Alongside this, testing procedures will be developed for the identification and diagnostic application of biomarkers, which allow the course of both the disease and therapy to be monitored. Furthermore, the department also houses the expertise required to create pharmacologically relevant in vitro and in vivo models.

Besides modern peptide synthesis and protein analytics methods (MALDI-TOF and LC-MS), the department has also developed a broad spectrum of biophysical methods for characterizing therapeutically relevant metabolic pathways, whose key proteins as well as cell-based and pharmacological models are used to characterize innovative chemical and biological agents.

UNITS

- Molecular Biotechnology, Dr. Holger Cynis
- Protein and Drug Biochemistry, Prof. Dr. Stephan Schilling
- Drug Design and Analytical Chemistry, Prof. Dr. Stephan Schilling (temp.)
- Protein Misfolding Diseases, Dr. Anja Schulze
- Astacin Proteases, Dr. Daniel Ramsbeck

CONTACT

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Further information on the department can be found in the full version of the annual report on pages 28–31.
https://s.fhg.de/iYj

POTSDAM-GOLM, BRANDENBURG, GERMANY

BRANCH BIOANALYTICS AND BIOPROCESSES

The Bioanalytics and Bioprocesses Branch in Potsdam-Golm was affiliated with the Fraunhofer Institute for Cell Therapy and Immunology on July 1, 2014. The site was initially founded in 2005 as a branch of the Fraunhofer IBMT and has since worked on technological solutions for biomedicine and diagnostics as well as for biotechnology and bioproduction.

The interdisciplinary team comprising natural scientists, engineers and technicians develops powerful, analytical methods for the detection and validation of pathogens and biological markers besides processes to obtain, handle and manipulate cells and biomolecules. In this context, the team develops applications for personalized medicine, as well as biosensors and detection procedures for the areas of agriculture and the environment, for a broad spectrum of substance classes.

The site has the state-of-the-art infrastructure required for miniaturizing and automating biological processes. This includes various biosensor and biochip technologies, pipetting robots and micro and nano-dispensers, besides many different rapid-prototyping procedures.

A further special feature of the branch's facilities is the life culture collection of cryophilic algae (CCCryo), which serves as a resource for developing production processes for novel, industrial bioproducts.

MANAGEMENT

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POTSDAM-GOLM, BRANDENBURG, GERMANY

DEPARTMENT OF BIOSYSTEM INTEGRATION AND PROCESS AUTOMATION

The department delivers solutions for complex laboratory automation tasks in biotechnology.

The department focuses on processes related to bioanalysis, diagnostics and cell culture, expansion, preparation and monitoring and aims at increasing the efficiency, quantity and quality of laboratory processes including cell products.

A further focal area is found in developing procedures and devices for a broad range of point-of-care applications. Among other things, an in vitro diagnostics (ivD) platform is available for this purpose, which can be adapted to different diagnostic tests depending on the task at hand.

Furthermore, procedures and devices are also available for analyzing and using molecular interfaces and higher-order electronic effects. Special importance is also assigned to developing procedures to gently dehydrate and fix dry reagents, which are used in all variants in diagnostics and analytics.

UNITS

- ivD Platform / PoC Technologies, Dr. Harald Peter
- Biomolecular Nanostructures and Measurement, PD Dr. Ralph Hölzel
- Biomimetic Functional Materials, Dr. Nenad Gajovic-Eichelmann
- Laboratory and Process Automation, Jörg Henkel

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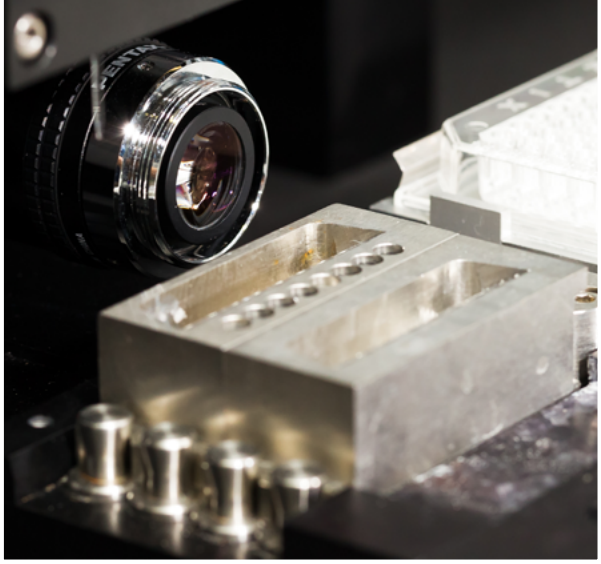
Further information on the department can be found in the full version of the annual report on pages 33–35.
https://s.fhg.de/T7F

POTSDAM-GOLM, BRANDENBURG, GERMANY

DEPARTMENT OF MOLECULAR UND CELLULAR BIOANALYTICS



The department deals to develop systems to detect, analyze and process challenging biological samples. These systems address demands in the fields of biomedicine, diagnostics, biotechnology, process control as well as environmental analytics, food safety and animal husbandry. The spectrum of solutions ranges from stand-alone sensor and fluidic components to integrated analysis systems and comprehensive database tools. The department develops point-of-care tests, e.g. for drug and serum screening, and likewise assays for the validation of biomarkers. Lab-on-a-chip systems for cultivating, processing and analyzing cell samples present a further focus. These chips allow long-term cultivation and toxicity tests on suitable cell clusters and micro-precise positioning of single cells or sorting heterogeneous cell populations. All of the department's activities are based on its profound expertise in sensor technology, spotting and dispensing technologies, surface coatings, microfluidics and the integration of functional units into all-in-one solutions. Its competence in molecular and cell biology allows the department to use its technological abilities in the most purposeful manner. Work can be carried out efficiently using the state-of-the-art instruments and facilities available in the department's well-equipped laboratories.

By integrating biobanks into so-called metabiobanks, the department provides solutions that facilitate and support the web-based case-by-case and sample-by-sample search for human biospecimens and associated data across institutional and national borders.

UNITS

- Microarray and Sensor Technology, Dr. Eva Ehrentreich-Förster
- Biomarker Validation and Assay Development, Dr. Harald Seitz
- Molecular Bio Engineering, Dr. Markus von Nickisch-Rosenegk
- Microsystems for In Vitro Cell Models, Dr. Katja Uhlig
- Microfluidic Cell Processing and Cell Analytics, Dr. Michael Kirschbaum

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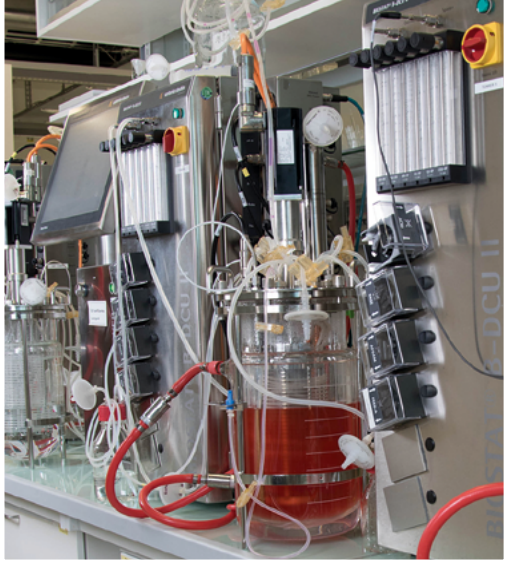
Further information on the department can be found in the full version of the annual report on pages 36–39.
https://s.fhg.de/b25

POTSDAM-GOLM, BRANDENBURG, GERMANY

DEPARTMENT OF CELL-FREE AND CELL-BASED BIOPRODUCTION



Conserving resources and creating efficient material cycles are two challenges currently facing the economy and technology. The sufficient and affordable availability of high-quality synthetic products is an important basis for making progress in the health care sector. Active agents and analytes, biomolecules such as enzymes, antibodies and aptamers often are key molecules of drug development in terms of diagnostics and therapy. But also in food and environmental technology, in the agricultural, cosmetics and detergent industries, the need for synthetic biomolecules is constantly on the rise. At present, many of these substances are manufactured using living cells and organisms. However, this is subject to considerable limitations. A sizable material and energy input has to be made to preserve cell metabolism itself. Beyond this, many metabolites, by-products and proteins, also in higher concentrations, are toxic to cells or organisms and can impede or even prevent these substances from being manufactured cost-effectively.

The cell-free bioproduction of high-quality proteinogenic biomolecules opens up completely new possibilities. By using the subcellular components of the organisms required for synthesis in suitable reaction environments it is possible to efficiently manufacture biomolecules with complex and also completely new properties. The technologies established at the Potsdam-Golm site allow these procedures to be used in an economically efficient way, thus creating a new basis for the economic production of active proteins.

The development, synthesis and also transfer of functional nucleic acids such as aptamers into market-relevant applications are a focus.

UNITS

- Cell-free Protein Synthesis, Dr. Stefan Kubick
- Eukaryotic Lysates, Doreen Wüstenhagen
- Functional Nucleic Acids – Aptamers, Dr. Marcus Menger

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Further information on the department can be found in the full version of the annual report on pages 40–42.
https://s.fhg.de/T4e

POTSDAM-GOLM, BRANDENBURG, GERMANY

EXTREMOPHILE RESEARCH & BIOBANK CCCRYO

The unit studies the adaptation strategies and industrial usability of cryophilic (= cold-loving) freshwater microalgae. The aim is to characterize these so-called snow and permafrost algae with regard to the various strategies by which they oppose extreme environmental parameters such as cold, UV radiation, drought and osmotic stress, before transferring these natural adaptation strategies into industrial applications. The CCCryo culture collection is unique in its diversity and scope and forms the basis of this work. Furthermore, the unit develops optimized photobioreactors for a sterile mass bioproduction of these autotrophic organisms on an industrial scale.

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Further information on the department can be found in the full version of the annual report on page 43.
https://s.fhg.de/bZG

ERFURT, THURINGIA, GERMANY

PROJECT CENTER MICROELECTRONIC AND OPTICAL SYSTEMS FOR BIOMEDICINE

The Microelectronic and Optical Systems for Biomedicine project center in Erfurt brings together the core competencies of three Fraunhofer institutes to span the disciplines of biosciences, microelectronics, microsystems technology, optics and photonics. This combined expertise will be used to develop application-ready systems in the areas of medical engineering, analytics, diagnostics, biotechnology, biophotonics, pharma, health care, ageing and food economics which will then be transferred into industry. Fields of application here include improved medical imaging and visualization as well as technologies for biomarker analysis.

INVOLVED FRAUNHOFER INSTITUTES

- Fraunhofer Institute for Applied Optics and Precision Engineering IOF (www.iof.fraunhofer.de/en)
- Fraunhofer Institute for Photonic Microsystems IPMS (www.ipms.fraunhofer.de/en)
- Fraunhofer Institute for Cell Therapy and Immunology IZI (www.izi.fraunhofer.de/en)

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CENTRAL FACILITIES & SERVICES

GLP TEST FACILITY

Good Laboratory Practice (GLP) describes a quality assurance system for conducting safety tests on chemicals, drugs, pesticides and food additives. It regulates the implementation, documentation, archiving and reporting of respective tests.

Fraunhofer IZI has been certified as a GLP test facility since 2009. The facility plans and conducts preclinical efficacy and safety studies for new drug candidates (especially ATMPs) and medical devices (ISO 10993) under GLP and GLP-analogous conditions. This involves developing and validating suitable in vitro and in vivo models. The test facility boasts a state-of-the-art setup for keeping small animals as well as small and large animal operating rooms. Furthermore, a broad spectrum of validated SOPs are implemented here for equipment and methods.

The test facility is currently certified for testing category 9. This includes, among other things, safety testing for ATMP immunotoxicity / immunogenicity, biodistribution and tumorigenicity in vitro and in vivo.

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GMP MANUFACTURING

GMP (Good Manufacturing Practice) describes a set of quality assurance guidelines for production and quality control processes and spaces with regard to drug manufacturing. It regulates, among other things, the requirements concerning hygiene, human resources, facilities, equipment, documentation and controls.

Fraunhofer IZI assumes the manufacture of investigational medicinal products for clinical trials. Manufacturing capacities here range from recombinant proteins over to so-called advanced therapy medicinal products (ATMPs). These include cell-based drugs such as gene therapeutics, somatic cell therapy medicinal products as well as tissue engineering products.

BIOPHARMACEUTICALS

In recent years, the increasing number of therapeutic monoclonal antibody (mAb) candidates under preclinical and clinical development have required new flexible, efficient, and economic opportunities for GMP production of therapeutic antibody candidates. Small-scale batch production of test samples for late preclinical GLP animal studies or for phase-1 and phase-2 clinical studies is often not appropriate for large-scale manufacturing facilities in the industry.

The clean rooms used for production of biopharmaceuticals cover a total area of 180 m² and comprise all clean room categories from D to A. The use of single-use equipment and materials enables an easy adaption to new process requirements. The GMP facility can be used for different contract manufacturing processes for preclinical and clinical (Phase 1 / 2) test samples as well as for process or instrument validation projects under consideration of special customer requests. The standard equipment can be easily adapted for new products. Besides the clean room facility, the institute operates a process development unit where relevant manufacturing processes are designed and upscaled and where respective quality control tests are established and checked for suitability. Alongside projects involving recombinant proteins, virus-associated projects can also be conducted here up to biosafety level 2.

The manufacturing team's portfolio includes transferring biopharmaceutical candidates from preclinical research into clinical development, drafting user-specific processes and manufacturing.

In summary the main advantages are:

- High flexibility
- Easy switch to different products
- Fast implementation of technology changes
- Customized production
- Ideal batch size for preclinical and early clinical trials
- Possibility to obtain ready-to-use GMP-compliant products by integrated sample filling

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ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPS)

The Fraunhofer IZI maintains three GMP-compliant clean room facilities. Through the flexible design, the facilities are especially attractive for companies that seek to bring newly developed medicinal products into clinical application via clinical trials. The facilities are divided into different independent suites. Each has its own grade C clean rooms (preparation), own air locks from grade C to B (personnel and materials transfer) and two grade B rooms (aseptic manufacturing). The clean room grade A is provided via laminar airflow cabinets that are installed in the B-rooms. The available clean room suites are specialized in conducting processes for manufacturing human autologous and / or allogeneic cell and gene therapeutic products (advanced therapy medicinal products). In addition to the clean rooms and the technical infrastructure, the Fraunhofer IZI offers assistance for the set-up and validation of GMP-compliant manufacturing processes as well as for obtaining a manufacturing authorization pursuant to section 13 of the German Drug Act (AMG).

WHY ARE GMP AND GLP IMPORTANT?

The clinical trial of new drug candidates is an essential step on the way to approval. Since the 12th revision of the "Arzneimittelgesetz AMG" (German Drug Act) every clinical trial must be approved of by the responsible higher federal authority ("Bundesinstitut für Arzneimittel und Medizinprodukte", Federal Institute for Drugs and Medical Devices, Paul-Ehrlich-Institut) and by the responsible ethics committee prior to the initiation of the clinical study. In order to obtain this authorization, the efficacy and safety of the investigational medicinal product must first be verified within the framework of GLP-compliant preclinical investigations (e.g. toxicological testing procedures). Furthermore, the quality of manufacture of the investigational medicinal products must be verified by a GMP manufacturing authorization pursuant to § 13 AMG. Relevant trial results from GLP-certified trial institutions and a GMP manufacturing authorization are thus absolutely prerequisite when applying for the clinical trial of a new medication.

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IMAGING AND IMAGE ANALYSIS

Phenotyping biological samples using multiple imaging methods forms a core competence of preclinical research. This enables thorough depiction, from the smallest structures (cell organelles) right through to entire organ systems, both in spatial and temporal resolution (4D).

Fraunhofer IZI has access to a comprehensive, state-of-the-art equipment pool that enables the acquisition and evaluation of various (also correlative) image data. Partners and customers are advised on biological, technical and economic matters and supported in carrying out and evaluating experiments. Furthermore, experimental procedures and equipment can be used, adapted and developed.

IN VIVO IMAGING

Magnetic resonance imaging (7 Tesla high-field small animal MRI)

- Examination of soft tissues and organs, use of contrast agents and cell labeling possible, long-term measurements in single individuals
- Depiction of anatomical changes, MRS, diffusion methods, functional imaging

Computer tomography (CT and X-Ray for small animals)

- Depiction of dense (bone, cartilage) and contrast-enhanced (soft tissue) structures
- 3D data sets can be used for conformal radiation treatment planning

Fluorescence and bioluminescence imaging for small animals

- Monitoring tumor growth and progression of inflammation, tracking cell movements following transplantation (cell tracking)
- Complex reconstruction of in vivo parameters by means of fluorescent imaging tomography (FLIT) or, in the case of bioluminescent sources, by means of diffuse light imaging tomography (DLIT) and spectral unmixing

Bedside imaging for small animals

- Various ultrasound units with a number of transducers and an implemented Color Doppler
- Flexible miniature cameras for the routine endoscopic examination of small animals and for the development of new lens attachments

IN VITRO / EX VIVO IMAGING

Clearing tissue samples
- Preparing samples for imaging (especially 3D fluorescence microscopy)
- Enabling detailed images of deeper layers of the sample that are usually only visible through histological sections

Confocal laser scanning microscope with live cell imaging
- Analysis of cell cultures and tissues in 4D, localizing target structures inside cells
- Standard laser lines from blue to red, water immersion lenses, real-time rendering and quantification of results

Light sheet microscopy
- Flexible light sheet microscope with modular sample chamber for sample sizes from just a few µm to 2 cm
- For the study of light-sensitive live-cell samples in high temporal resolution

Atomic force microscopy
- Nanometer-scaled, micro-mechanical sampling of surfaces using a cantilever measuring needle and measurement of the occurring atomic forces

MALDI Mass Spectrometry Imaging (MALDI-MSI)
- Label-free methods of depicting the distribution of macro molecules in histological samples based on their degree of ionization and time of flight (TOF) in the electric field; special sample preparation and matrix application required, statistical evaluation of distribution patterns

Laser capture microdissection
- Isolating individual cells or tissue structures by means of microscopic laser cuts, analyzing samples using molecular biology methods (RT-PCR, proteomics)

Hardware-linked evaluation process
- Stereological quantification using the upright fluorescence and reflected-light microscope for unbiased histological evaluations
- Virtual microscopy in order to create completely virtual tissue sections for digital post-processing, high-throughput technique

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CENTER FOR EXPERIMENTAL MEDICINE

The development of new drugs entails testing using suitable animal models. Animal experiments are therefore an integral component in the development of new drugs, therapies and diagnostic procedures. The institute's Centre for Experimental Medicine (TEZ) is a central unit which facilitates important steps in translating research findings into a clinical application for human subjects.

Moreover, the institute has access to one of the most state-of-the-art animal houses in Germany. The TEZ is distinguished by its highly technical facilities, which are optimized to handle preclinical research projects. These facilities include modern rooms in which the animals are kept, featuring standardized hygiene levels and individually ventilated cage systems that are monitored via the building management system.

The health and care of the animals is of the highest priority. Highly qualified personnel support the scientific staff in daily care, health monitoring and breeding activities, and in administering treatments.

All experimental work can be carried out under practically sterile conditions. Several fully fitted operating suites allow small and large animals to be examined and treated. The comprehensive, state-of-the-art equipment guarantees correct anesthesia, analgesia and species-relevant blood analyses.

An expansive equipment pool for imaging technologies at the institute enables partly non-invasive analysis methods and also contributes towards reducing the need for animal experiments. This means, for example, that in vivo imaging analyses can be carried out using, for instance, 7 Tesla magnetic resonance imaging, bioluminescence imaging or small-animal CT.

In order to work on a range of issues, the TEZ has access to areas approved for genetic engineering safety levels S1 to S3; it may also conduct in vivo studies in line with GLP (Good Laboratory Practice).

The TEZ forms the central interface at the institute for processing preclinical development projects. Furthermore, cooperation projects with external clients and other research institutes are also carried out. At the same time, the TEZ acts as a training facility for animal care supervisors in a research and clinical setting, also offering advanced training courses for experimenters.

Adherence to the animal welfare guidelines is strictly monitored by the institute's animal welfare officers and regularly controlled by the regional animal welfare authority.

EQUIPMENT AND SERVICES:

- Small animals are kept under state-of-the-art standards and permanently monitored
- Animal husbandry under GLP standards
- Animal husbandry with the option to use infecting agents for experimental infection

- Quarantine services
- Standard in-breeding and breeding transgenic lines
- Operation units in various areas including provision of inhalation anesthesia for small and large animals

- Large-animal OP area with intensive care capacity
- C-arm
- Option for individual stereotactic brain surgery
- Autopsy room for large animals
- Intraoperative blood gas analyses

- Small animal endoscope
- Blood cell meter
- Surgical microscope
- Stereotactic manipulation
- Temperature control during operations

- In vivo bioluminescence
- Small animal magnetic resonance imaging
- Small animal computer tomography
- X-ray unit for whole-body irradiation and pinpointed radiation therapy
- Large capacity autoclave
- Sterilization units using hydrogen peroxide fumigation
- Cryopreservation of spermatozoa and embryos
- Tissue bank

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RIBOLUTION BIOMARKER CENTER

The Biomarker Center received a new seal of quality in June 2020. Following successful certification by TÜV Rheinland, a quality management system was established in accordance with ISO 9001:2015 under the direction of Professor Friedemann Horn, Dr Conny Blumert (Next-Generation Diagnostics Unit) and Dr Kristin Reiche (Bioinformatics Unit).

In the Biomarker Center, new diagnostic and prognostic RNA biomarkers are systematically and comprehensively identified and validated using cutting-edge technologies such as next generation sequencing (NGS). Expertise in managing studies and data is essential when it comes to planning and arranging clinical cohorts as well as handling clinical and experimental data. The biomarker screening process is also being optimized and perfected with the aid of technical innovations. Since June 2020, the procedures involved here have been governed by a certified quality management system (ISO 9001:2015).

The TÜV certificate specifically covers: "Research and commissioned work in the field of molecular diagnostic analytics and the related bioinformatic evaluation, with emphasis on personalized medicine as well as optimizing and developing modern processes and applications for molecular diagnostics including next generation sequencing". The appraised quality management system ensures that internal operations, service quality, and partner and customer relationships are all overseen by a quantifiable system at the Biomarker Center. This means that processes are mapped precisely, their efficiency increased, and internal errors reduced. Process validation is another important aspect at the Biomarker Center. If a process is documented, evidence can always be provided to show that it fulfills the demands placed on a particular service and that it delivers reliable, transparent results. This enables competitive research and development projects to be driven forward together with clinical partners and interested research partners.

Zertifikat

Prüfungsnorm ISO 9001:2015

Zertifikat-Registrier-Nr. 01 100 2000010

Unternehmen: **Fraunhofer-Institut für Zelltherapie und Immunologie**
RIBOLUTION Biomarker Center
Perlickstr. 1
04103 Leipzig
Deutschland

Geltungsbereich: Forschung und Auftragsarbeiten im Bereich molekulardiagnostischer Analytik und ihrer bioinformatischen Auswertung, mit Schwerpunkt auf personalisierter Medizin, sowie Optimierung und Entwicklung moderner Prozesse und Anwendungen für die Molekulardiagnostik inklusive Next-Generation Sequenzierung

Durch ein Audit wurde der Nachweis erbracht, dass die Forderungen der ISO 9001:2015 erfüllt sind.

Gültigkeit: Dieses Zertifikat ist gültig vom 23.07.2020 bis 22.07.2023.

10.08.2020

TÜV Rheinland Cert GmbH
Am Grauen Stein · 51105 Köln

www.tuv.com

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S3 SAFETY LABORATORY

Fraunhofer IZI operates a safety level 3 laboratory, making it possible to handle research and development projects under biosafety level 3 conditions and to investigate highly pathogenic agents. Genetic engineering work can also be undertaken. Adjacent premises for keeping animals permit the development of and work with infection models for corresponding types of pathogen.

Safety precautions taken in the S3 laboratory include an independent ventilation system with separate filters (H14 class HEPA filters) for all rooms incl. autoclave. High-efficiency particulate air filters eliminate 99.995 percent of all particles measuring between 0.1 and 0.3 micrometers. The ventilation system guarantees eight air changes per hour with an air flow volume of up to 1500m³/h air throughput.

Airlocks and pressure differences between areas prevent infectious particles from escaping into the air. Every room can also be aerated and ventilated separately to eliminate contamination.

Staff safety is ensured through specific training measures, special safety clothing and protective hoods with integrated air filter systems.

FACILITIES

The S3 laboratory is equipped with a safety cabinet, various centrifuges, an inverted microscope with phase contrast, a refrigerator, a -80°C ultra-low freezer, an incubator and a thermal cycler for cellular and molecular biology work.

Standard activities include using cell cultures for virus propagation, using assays to determine viral concentration (TCID50, plaque assay), and virus inactivation. Neutralization assays can also be carried out.

The laboratory is currently being used to examine viruses transferred by arthropods such as the dengue or West Nile viruses alongside SARS-CoV-2. Other pathogens that fall under biosafety level 3 can be added as required.

ACHIEVEMENTS AND CONTRACT RESEARCH

- Testing and developing drugs in vitro and in vivo
- Testing and developing vaccines
- Immunology studies (e.g. analyzing protective antibodies from patients), also in cooperation with hospitals
- Material testing (e.g. antiviral coatings)
- Testing disinfectants
- Virus stability testing
- Establishing infection models on lab-on-a-chip technologies

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SELECTED PROJECTS

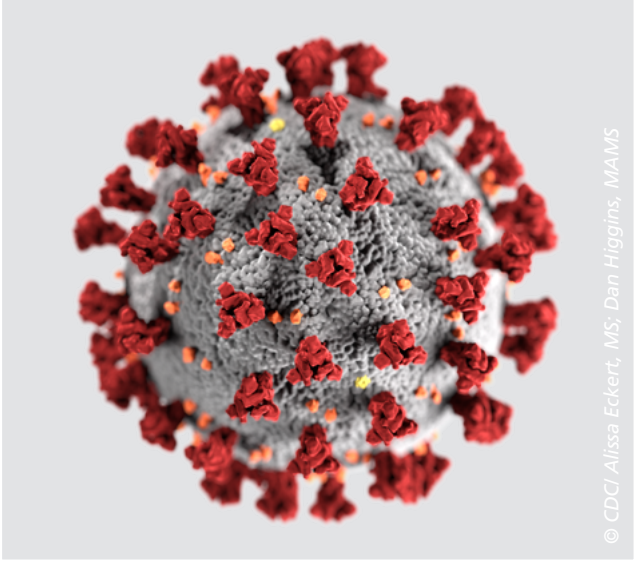
CORONA PANDEMIC

United against corona – Fraunhofer experts are on the front line in the fight against Covid-19, helping the economy and society to overcome the immediate effects and future consequences of the pandemic.

Fraunhofer IZI is involved in various projects aimed at investigating, developing and optimizing solutions for diagnostic, preventive and therapeutic procedures. Infection models and work in the S3 safety laboratory (see page 40), where research can be conducted using the active SARS-CoV-2 virus, form a focus here.

The majority of projects are largely funded through the Fraunhofer-Gesellschaft's own resources.

CORONA PANDEMIC



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SWAB-FREE – INFECTION PREVENTION THROUGH SMEAR-FREE ON-SITE TESTING FOR SARS-COV-2

Developing an apparatus-free respiratory gas analysis for the preventive monitoring of health status, especially for people in "system relevant" professions. This involves integrating a sensory breath analysis into face masks for virus detection.

BEAT-COVID – THERAPEUTIC STRATEGIES AGAINST COVID-19

Developing novel therapeutic strategies to inhibit the entry of SARS-CoV-2 into respiratory epithelial cells and developing a therapy to inhibit the excessive immune response of Covid-19 through the inhalation of anti-inflammatory antibodies.

ANTICOV – CELL-FREE PROTEIN SYNTHESIS AS A RAPID RESPONSE TO COVID-19

Conducting a feasibility study to qualify cell-free protein synthesis as a platform technology for the rapid synthesis of viral proteins expressed by SARS-CoV-2, including potential mutations.

C19 LUNG CHIP – DRUG REPURPOSING USING A COVID-19 INFECTION MODEL

Establishing a Covid-19 lung infection model (lung-on-chip) which simulates the pathogenesis of Covid-19 in order to test the effectiveness of up to 40 different substances or substance combinations against SARS-CoV-2.

CORONASENSE – COVID-19 PEPTIDE-BINDING ANALYSIS FOR DIAGNOSTICS AND TREATMENT

Determining the binding kinetics of multivalent bonds that emerge on the spike proteins found on the surface of SARS-CoV-2. Diagnostic exploitation of the invention of a nanostructure with a nucleic acid scaffold and virus-binding peptide moieties.

COROVACC – DEVELOPING A SARS-COV-2-SPECIFIC VACCINE

Developing a SARS-CoV-2-specific vaccine virus based on an established platform vector (herpes virus derivative).

COVER-AB – HUMAN ANTIBODIES AGAINST SARS-COV-2

Extracting human monoclonal and neutralizing antibodies against SARS-CoV-2 to begin with, checking for their anti-viral effectiveness in cell cultures and examining a selection in a transgenic mouse and rhesus monkey model. The envisaged antibodies would permit passive vaccination in humans.

SPONSORED BY THE

Federal Ministry
of Education
and Research

COVIDVAL – CLINICAL STUDY INTO THE USE OF ACE INHIBITORS AS A TREATMENT OPTION FOR COVID-19

Examining whether antibodies are present in Covid-19 patients' serums which, in the event of a Covid-19 infection, block other important molecular structures in addition to blocking the known ACE2 / TMPSSR binding site. Their existence could possibly explain the extremely varied individual courses of the disease.

This project is co-financed by tax revenues on the basis of the budget approved by members of the Saxon state parliament.

COV-TOT – EXAMINING THE IMPACT OF VIRUS INACTIVATION ON THE EPITOPE SPECTRUM IN (COVID-19) SERUMS

This project was able to show that different methods of virus inactivation have a varying impact on different antibodies in the sera. This exacerbates reproducibility and the establishment of epitope-based diagnostics and can, in individual cases, lead to completely different results in serological tests. A slight denaturation of the sample also appears to prevent individual antibodies from being blocked by unknown serum components. There is therefore scope to obtain better results. Two suitable methods of virus inactivation have been identified: firstly heating to 56 degrees Celsius for ten minutes for liquid samples, and secondly treatment with 70% ethanol when antibodies are immobilized on protein A.

DEFEND-COV2 – TESTING VACCINES AND ACTIVE AGENTS AGAINST SARS-COV-2

Creating an infrastructure for testing and evaluating vaccines and active agents against SARS-CoV-2 that also allows rapid production for preclinical testing and further GMP-compliant clinical development.

DISCOVER 21 – HIGHLY SENSITIVE LATERAL FLOW SYSTEMS FOR DETECTING VIRAL PATHOGENS

Developing a diagnostic test based on PCR-free detection. The project aims to produce highly sensitive lateral flow test strips on which the target substances are directly and specifically detected. This would eliminate lengthy analysis steps such as the transcription of RNA into DNA and the subsequent PCR.

DRECOR – DRUG REPURPOSING FOR CORONA

Generating and testing candidate molecules formulated for inhalative or systemic administration via the airways, as well as developing a device prototype for clinical development.

EPICOV2020 – SARS-COV-2-SPECIFIC SEROLOGICAL DIAGNOSTICS BASED ON EPITOPES

Identifying epitopes, i.e. the binding sites on coronavirus proteins recognized by patient antibodies, that lend themselves to the specific detection of antibodies against various coronaviruses and transferring the findings into a test procedure suitable for practical use with a high degree of specificity.

SPONSORED BY THE

Federal Ministry of Education and Research

SENSE-COV2 – ANALYZING THE INNATE IMMUNE RECOGNITION OF SARS-COV-2 USING RECOMBINANT VIRUSES

Characterizing mechanisms that enable SARS-CoV-2 to go undetected by the human innate immune system. Providing a foundation and new target structure for the possible development of antiviral drugs aiming at improved control of the virus by the innate immune system.

SPONSORED BY THE

Federal Ministry of Education and Research

SAXOCOV – SAXON COVID-19 RESEARCH CONSORTIUM OF NON-UNIVERSITY, UNIVERSITY AND CLINICAL PARTNERS

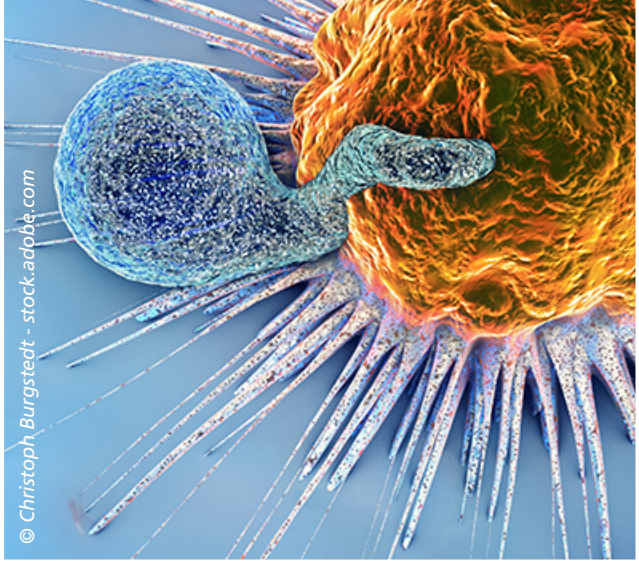
Conducting a diagnostic field study on the spread of SARS-CoV-2 in order to follow the development of the SARS-CoV-2 epidemic in the Free State of Saxony on multiple levels.

This project is co-financed by tax revenues on the basis of the budget approved by members of the Saxon state parliament.

VIRENWOLF – VIRUCIDAL TUNGSTEN CARBIDE-BASED COMPONENT SURFACES FOR INTENSIVE MEDICAL AND NURSING CARE FACILITIES

Developing tungsten carbide coatings with copper-containing solution-resistant binders besides testing their virucidal effectiveness and examining potential cytotoxic effects with regard to the compatibility of people handling them. The project aims to produce inexpensive abrasion-resistant virucidal and antibacterial surfaces.

IMMUNO-ONCOLOGY



MANUFACTURE OF KYMRIAH®

CAR-T cell therapy is a new type of cancer immunotherapy whereby patients' immune cells are genetically modified so as to recognize cancer cells and instigate their destruction. The drug was manufactured in the clean rooms at Fraunhofer IZI for Novartis Pharma AG as part of a clinical trial. Approval was granted by the European Commission in summer 2018.

ROR1 CAR-T POC INITIATIVE

The chimeric antigen receptor (CAR) developed at the University Hospital of Würzburg recognizes the ROR1 molecule, which is expressed in cancer cells in leukemia, for example, as well as in breast and lung cancer. As part of the project, preclinical trials are to be conducted into the safety and efficacy of the ROR1 CAR-T cells and clinical translation is to be driven into a phase I/II study (first in human). The project is being funded under the proof-of-concept initiative instituted by the Fraunhofer-Gesellschaft, the Helmholtz Association and Deutsche Hochschulmedizin.

Sub-project preclinical GLP study

Central facilities and services: GMP manufacturing

Central facilities and services: GLP test facility

IMAGE-BASED, HIGH-THROUGHPUT CELL SORTING

Establishing a flow method for the image-based, high-throughput sorting of cells that builds on globally unique microfluidic systems. The procedure is to be used to isolate rare immune cell stages that are important for anticancer immunotherapy in order to perform genome analyses on single cells.

INFECTION RESEARCH

WORKING WITH HIGHLY PATHOGENIC VIRUSES

Fraunhofer IZI has operated an S3 laboratory since 2016, where work is carried out using highly pathogenic disease agents such as the West Nile, dengue and Chikungunya viruses. Since March 2020, a huge amount of work has also involved the novel coronavirus SARS-CoV-2. Besides testing the efficacy of vaccines and drugs and verifying the antiviral effect of certain materials used, for instance, in means of transport and hospital facilities, research is also focused around the immune response of Covid-19 patients. As an airborne pathogen, SARS-CoV-2 places even higher demands on safety in the laboratory.

BREATHALERT – TRACKING DOWN ANTIBIOTIC-RESISTANT BACTERIA USING ION MOBILITY SPECTROMETRY

A new procedure is being established for the rapid and non-invasive detection of infecting agents and existing antibiotic resistances in breathing air. An enhanced form of ion mobility spectrometry is to be used to characterize volatile organic compounds (VOCs) from microorganisms. Investigations will look at whether these can be differentiated via the emitted VOCs and assigned to the respective type of bacteria. Characterizing clinical isolates, taking respiratory air samples from infected patients, and measuring the impact of, for example, dietary habits on human respiratory air round off the project.

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DEVELOPING BOTANICALS-BASED PESTICIDES TO FIGHT PHYTOPATHOGENIC FUNGI IN AGRICULTURE

Together with Makerere University (Kampala, Uganda) and the IRGIB (Cotonou, Benin), extracts were taken from the leaves, fruits and barks of tropical plants and tested both in vitro on various harmful fungi species as well as ad planta. In some cases, the effect of these plant extracts was actually superior to that of commercial agents, especially in fighting resistant and multiresistant harmful fungi. Moreover, the

tested botanicals demonstrate good rain resistance and high UV stability. Utilization strategies for sustainably produced and ecologically compatible pesticides will now be developed together with the African partners.

Federal Office for Agriculture and Food

GLYCO3DISPLAY: DNA-BASED ARRANGEMENT OF GLYCANS FOR DEVELOPING NEW PATHOGEN ANTI-ADHESIVES

Pathogenic bacteria and viruses use glycans, i.e. long and complex sugar molecules, to recognize, bind to, and infect host cells. Nanometer-scale geometry plays a vital role here. By combining Fraunhofer IZI's DNA nanotechnology with the automated glycan synthesis available at the Max Planck Institute of Colloids and Interfaces, novel compounds can be created based on carbohydrates. These are precisely arranged, defined glycan chains with a spatial resolution of a single nanometer. In addition, a high-throughput assay will be established to investigate the binding of specific glycans and their isomers to target pathogens or to sugar-binding proteins.

INVESTIGATING THE INFECTIVITY OF DIFFERENT PATHOGENS USING A LOW-DOSE INTERLEUKIN-2 IMMUNOTHERAPY FOR LUPUS ERYTHEMATOSUS

IL-2 therapy aims at regulating Treg cell numbers and is a promising form of treatment for the autoimmune disease systemic lupus erythematosus (SLE). Regulatory T-cells (Treg) in particular are known to play a central role in maintaining immunological tolerance. Too few increases susceptibility to autoimmune diseases, while too many can result in an increased susceptibility to infection. The safety of the IL-2 therapy is to be tested with respect to an increased susceptibility to infection based on an in-vivo model. The long-term goal is to create a prediction platform for different pathogens in patients receiving IL-2 therapy.

FURTHER SELECTED PROJECTS

3D RENAL TISSUE MODELS

Tissue model systems are to be established to delve deeper into a range of issues relating to the efficient decellularization and subsequent recellularization of rat kidney tissue. The application of hydrostatic high-pressure treatment (HHP) on the decellularization process will be examined for the very first time. HHP may result in an extremely rapid and effective devitalization of the cells, making subsequent perfusion shorter and therefore less damaging on the extracellular matrix (ECM). Besides intact kidneys, precision cut kidney sections will also be examined as they are extremely well suited as 3D tissue model systems.

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ANTIBODIES FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

The overwhelming majority of neurodegenerative diseases are attributed to the misfolding, i.e. structural change, of proteins. This causes a deposit, which damages the surrounding tissue and nerve cells and eventually causes them to die off. The therapeutic goal is to prevent peptides from being deposited and/or to accelerate the breakdown of the respective proteins. The project aims to isolate specific antibodies that bind and break down only the modified protein. Effective candidates are to be selected from a range of antibodies to prepare the molecules for human use.

AUTOMATED ANALYSIS OF PEPTIDE MICROARRAYS

During the development of particularly sensitive microarray test systems, prototypes can often contain just a few positive signals and also have a very low signal-to-noise ratio (SNR). Algorithms featuring a particularly robust detection and segmentation of spots are being developed for the high-throughput analysis of these kinds of images. These have

already been successfully tested on images taken from allergy research. The aim is to evaluate other use cases and to implement the algorithms in a distributable software.

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DETERMINATION OF PHARMACOKINETIC PARAMETERS OF SMALL MOLECULES

The preclinical development of small molecules first requires their comprehensive characterization with regard to physico-chemical, cell biological and pharmacokinetic properties. This should ensure that effective, safe and well tolerated drugs are ultimately administered to humans that fulfill the requirements of the respective clinical picture.

A catheter-based test procedure will be established within the project to determine pharmacokinetic properties of small molecules in experimental animals. This procedure makes it possible to gain complete drug profiles from a single individual, thus reducing the number of animal experiments needed in drug development.

The described procedure is being used, among other things, to develop alternative beta-secretase inhibitors and to develop novel drugs for treating periodontitis.

BROADENING THE CHEMICAL SPACE OF METAL BINDING GROUPS

Developing a computational chemistry approach that makes it possible to significantly expand the chemical space of metal binding groups. Fragments discovered here are adapted for the respective application and constitute completely new chemical classes of molecules for future medicinal-chemical development. In the case of one particular metal-dependent acyltransferase, for example, six yet unspecified and just as active compound classes were able to be identified and pursued further. This should avoid the possible adverse effects of potential new drugs described in the literature for the metal binding groups used to date.

SERA MAPPING FOR EPITOPES OF ALLERGY ANTIBODIES

Projects are aimed at identifying the specific binding sites of allergy-relevant antibodies in allergenic food proteins with the goal of understanding their formation as well as cross reactions with other allergens. Respective epitopes have already been identified for many important food allergens such as nuts, legumes and wheat. The research conducted here facilitates more precise immunological detection, improved food processing and hopefully, in the near future, also a prognosis as to the severity of an allergy.

miRNA ANALYSIS OF PATIENTS WITH CHRONIC PAIN

Characterizing miRNA in serum samples obtained from polyneuropathy and/or radiculopathy patients. By measuring specific electrophysiological profiles for the early detection of functional disorders affecting the sensory system, patients can be specifically classified and assigned to corresponding groups. This allows single analytes or groups of analytes to be identified, e.g. miRNA or cytokines. Following the bioinformatic evaluation of the data, specific markers can be pinpointed and transferred to a potential platform for point-of-care analysis.

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PROCESS DEVELOPMENT, MANUFACTURING AND QUALITY CONTROL FOR A CHIMERIC FICOLIN-ANGIOPOIETIN FUSION PROTEIN

Many current treatments for Covid-19 and similar infectious disease are focused around antiviral approaches. Use of the recombinant protein (Ang1 mimetic) developed by the company Mannin Inc. offers a host-associated approach and aims to stabilize the endothelium, which would reduce the

impact of acute respiratory distress syndrome (ARDS). The project sets out to establish a GMP-compliant manufacturing process for the fusion protein Ang1 mimetic, including the necessary quality controls, thus facilitating the biomolecule's clinical application.

NON-DESTRUCTIVE TEST AND MEASUREMENT METHODS IN THE BIO-NANOTECHNOLOGY APPLICATION LABORATORY

Establishing non-destructive test and measurement methods for analyzing the effects of cell-material interactions.

FURTHERANCE

SPONSORS AND ADVISORY BOARD

The support and commitment of active institutions and individuals enable the Fraunhofer IZI to experience continuous and successful development as well as dynamic growth.

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The Fraunhofer IZI would like to thank the European Union, the Federal Ministry of Education and Research, the Free State of Saxony and the City of Leipzig via the Leipzig Foundation for Innovation and Technology Transfer for their financial support.

The European Union sponsors through the programs EFRE and ESF. The building projects of the Fraunhofer IZI are sponsored 60 percent by the European Union and 20 percent each by the Federal Ministry of Education and Research and the Free State of Saxony. The plot of land is provided by the City of Leipzig in hereditary leasehold and free of charge. Furthermore, Fraunhofer IZI would like to thank the Leipzig Foundation for Innovation and Technology Transfer for its support during the institute's construction phase from 2005 to 2010.

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THE FRAUNHOFER-GESELLSCHAFT

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Typesetting & layout
Michaela Grunert

Translation
LSI World of Languages GmbH

Photo acknowledgements
Unless otherwise indicated all pictures and figures
© Fraunhofer IZI

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Printed by
Druckerei Gebr. Pape
Jühengrund 24, 33142 Büren, Germany

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