

Fraunhofer IZI

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# Annual report 2022/2023



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# Portrait of the institute

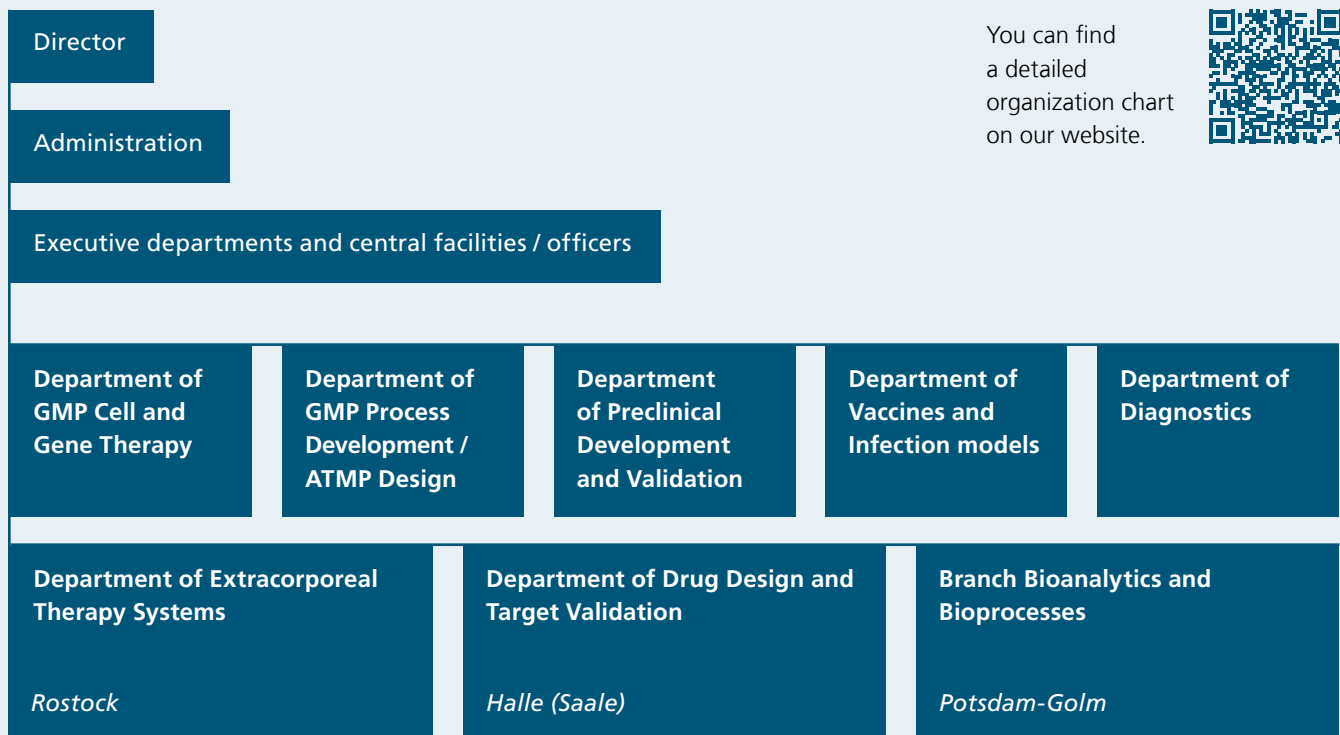
The Fraunhofer Institute for Cell Therapy and Immunology IZI investigates and develops solutions to specific problems at the interfaces of medicine, life sciences and engineering. One of the institute's main tasks is to conduct contract research for companies, hospitals, diagnostic laboratories and research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

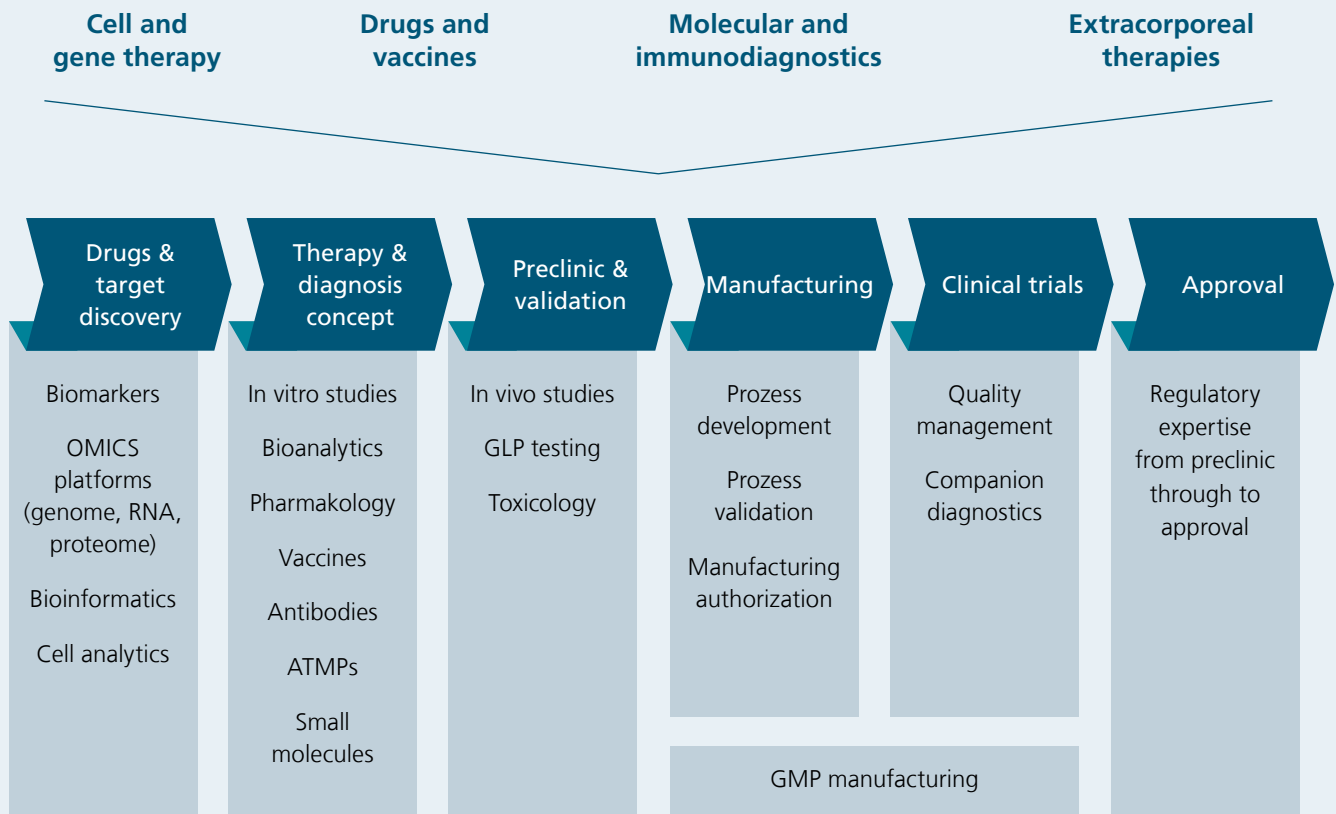


You can find a detailed organization chart on our website.





# Business units and competencies





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## Research area immuno-oncology

For a few years now, immuno-oncology has been complementing the classic methods of cancer therapy, radiotherapy, chemotherapy and surgery. Here, medicine makes use of the natural function of the immune system to eliminate foreign and degenerate cells via a wide variety of mechanisms. With the research area immuno-oncology, Fraunhofer IZI supports partners in the development and translation of innovative immunotherapies.

### R&D focus

- ATATMP development
- Preclinical development of cell and gene therapies (efficacy and safety analysis)
- Cell analysis, assay development and diagnostics
- GMP process development / process transfer
- Manufacturing of clinical investigational medicinal products



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## Research area infectious disease pathology

Infectious diseases continue to pose a global threat to human and animal health. Understanding the spread, pathogenesis and possibilities of diagnosis, is essential for their effective control. With the research area infectious disease pathology, Fraunhofer IZI supports partners in the development and translation of technologies for research, diagnostics, prevention and therapy of infectious diseases.

### R&D focus

- Preclinical development of active agents and vaccines (efficacy and safety analysis)
- Vaccine technologies
- Drug and material testing
- Assays and diagnostics



# Research infrastructure at the Leipzig site

Isotope laboratory

GMP facilities

Animal husbandry incl. small and large animal OP and small animal MRI

Transparent prototyping laboratory

S3 laboratory

Seminar area and cafeteria

## Buildings

### Main building

- Usable area: 4 131 m<sup>2</sup>
- Lab space: 1 867 m<sup>2</sup>
- Offices: 1 615 m<sup>2</sup>
- Seminar area: 276 m<sup>2</sup>

### First extension building

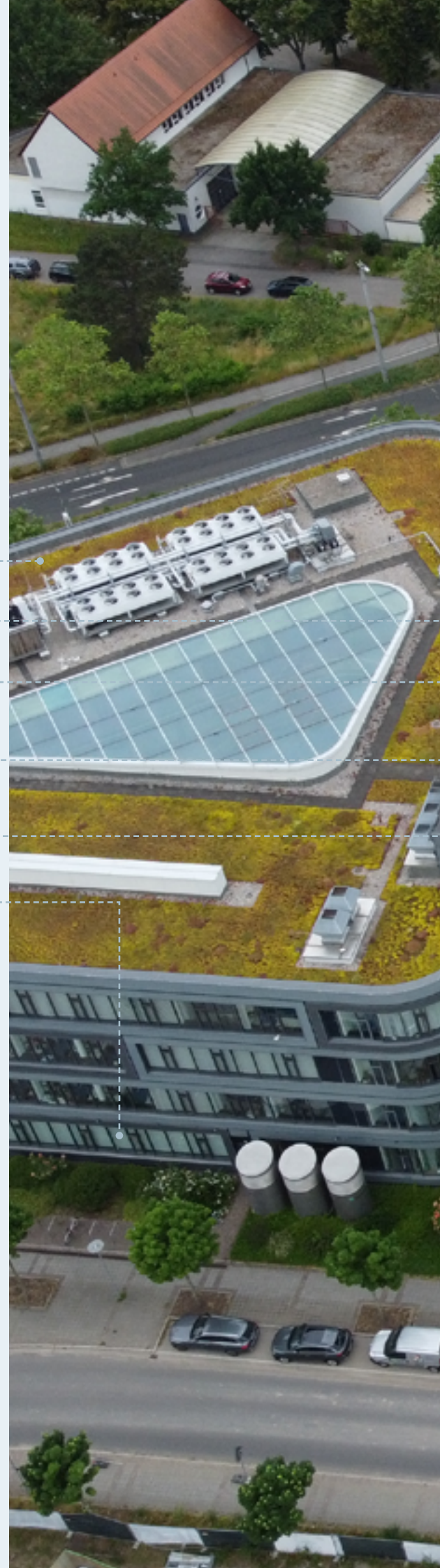
- Usable area: 1 568 m<sup>2</sup>
- Lab space: 470 m<sup>2</sup>
- Offices: 142 m<sup>2</sup>
- Clean rooms: 410 m<sup>2</sup>

### Second extension building

- Usable area: 3 050 m<sup>2</sup>
- Lab space: 1 171 m<sup>2</sup>
- Offices: 881 m<sup>2</sup>
- Clean rooms: 402 m<sup>2</sup>

### Rental area at BIO CITY Leipzig

- Clean rooms: 334 m<sup>2</sup>





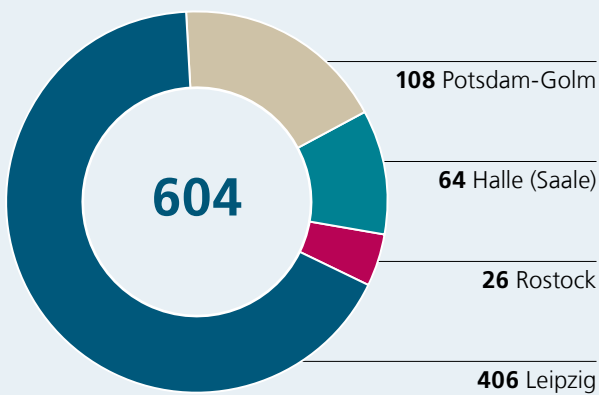




# Key institute figures 2022

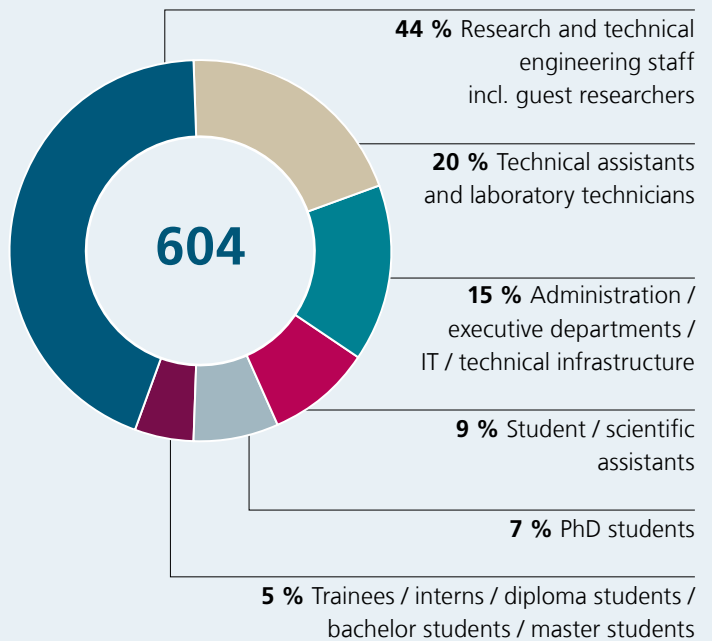
## Employees

by location



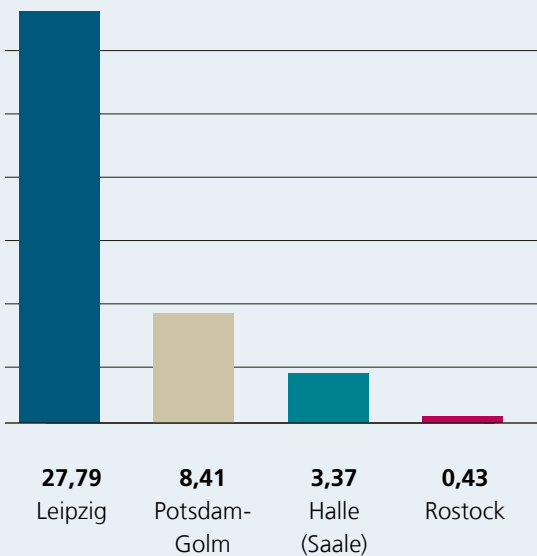
## Employees

workforce composition



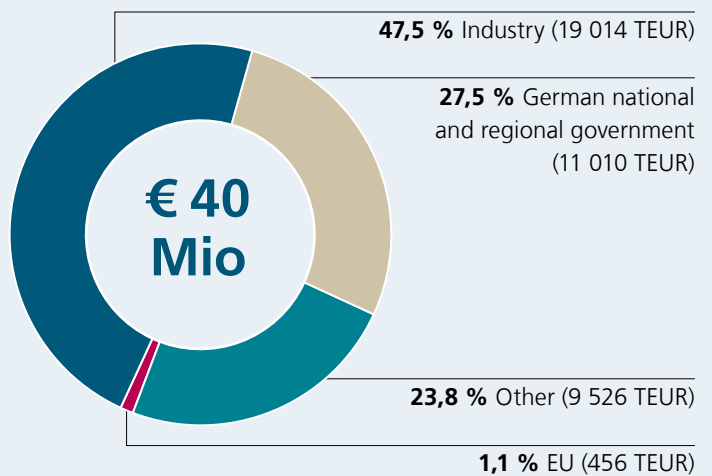
## € 40 Mio project revenue

by location in € mio



## Project revenue

by funding agency



December 31, 2022

## Scientific presence and network 2022



**129** **150**

Industry partners

Research partners



**~60**

Patent families

with approx. **300** patents & patent applications



**106**

Conventions & conferences



**59**

Evaluator activities



**97**

Association memberships in various expert associations

**93**



Publications

**2**

Book articles

**96**

Abstracts



**64**

Teaching activities

**25**



Graduation publications

5 doctorates | 1 diplom theses  
13 master theses | 6 bachelor theses



Detailed information on the key figures and publications can be found on our website at [www.izi.fraunhofer.de/en/publications](http://www.izi.fraunhofer.de/en/publications)







# Locations and departments

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**Leipzig, Saxony, Germany**

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## 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 Vaccines, 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 m<sup>2</sup>.

### Management

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## Leipzig, Saxony, Germany

# Department of GMP Cell and Gene Therapy

The Department of GMP Cell and Gene Therapy operates Fraunhofer IZI's two modern GMP facilities consisting of six separate clean room suites (altogether 13 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 105 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.

### Core competencies

- Manufacturing and quality control of ATMPs
- Manufacturing authorization according to §13 AMG
- GMP process and method transfer
- Good Manufacturing Practice (GMP)
- ATMPs
- 632 m<sup>2</sup> clean rooms
- Quality assurance
- Investigator Medicinal Product Dossier (IMPD)

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## Leipzig, Saxony, Germany

# Department of Cell and Gene Therapy Development



as clinically relevant application aspects are considered at all stages of development.

In addition, biomolecules such as antibodies, proteins, enzymes and, in the future, viral vectors are produced in pharmaceutical quality in a separate GMP manufacturing unit.

After successful process optimization, investigational medicinal products can be produced by the Department of GMP Cell and Gene Therapy and further accompanied until approval.

### Core competencies

- GMP process development and transfer for cell and gene therapy manufacturing
- mRNA technology
- Specialist expertise in hematology / oncology
- Process optimization and automation
- Good Manufacturing Practice (GMP) evaluation for cell and gene therapy manufacturing
- Quality assurance
- GMP-compliant equipment and processes
- Clinical trial planning
- CAR-T/NK cells and NK cell technologies
- Biomaterials research
- Non-clinical developments (in vitro and in vivo)
- Preparing GMP documents (SOPs, batch records, quality control records...)
- GMP process development for biopharmaceuticals
- GMP certification
- Manufacturing authorization for therapeutic antibodies pursuant to Section 13 (1) of the German Medicinal Products Act (AMG)

The Department of Cell and Gene Therapy Development researches and develops cell and gene therapy technologies and realizes the transfer of manufacturing processes from an experimental stage to GMP-compliant procedures.

The focus is on antigen-specific T cells, CAR T cells, CAR NK cells, dendritic cells, mesenchymal stromal cells and tissue engineering products.

The department's competencies, which build on each other, include research and development, preclinical evaluation and GMP process development for cell and gene therapies up to transfer into pharmaceutical manufacturing processes. Manufacturing parameters and quality controls can be tested and optimized flexibly and cost-efficiently.

New technologies (including digitalization, artificial intelligence, automation) as well

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## 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 Fraunhofer 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, preclinical studies (even those in other Fraunhofer IZI departments) can be performed under GLP.

### The department covers the following topics

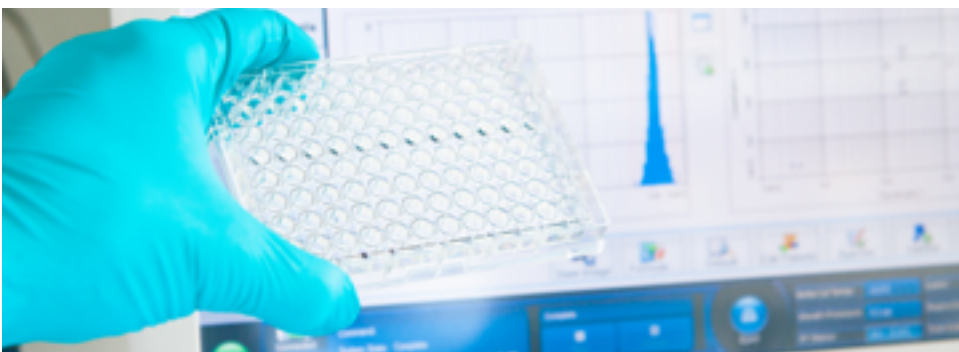
- Planning and execution of preclinical efficacy and safety studies for new drug candidates (especially ATMPs) and medical devices (ISO 10993) under GLP or GLP-analogous conditions. This includes the development and validation of suitable in vitro and in vivo models.
- Developing procedures for the diagnostic 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 regenerative medicine.
- 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.

### Core competencies

- Preclinical studies
- Good laboratory practice (GLP)
- Immunotoxicology (study design and implementation)
- Efficacy and safety studies for ATMPs and class-3 medical devices
- Protein biomarker (identification and validation)
- Antibody development (therapy)
- Antibody and immunoassay development (diagnostics)



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## Leipzig, Saxony, Germany

# Department of Vaccines and Infection Models

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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.

### Core competencies

- Vaccine development
- Infection models
- Inactivation of pathogens
- Working with highly infectious pathogens
- Drug testing
- Antimicrobial therapies





## 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.



### Core competencies

- Transcriptome and immunome analyses
- Next-generation-diagnostics
- Bioinformatics
- Nanotechnology
- Lab-on-chip
- Biomarker identification
- Tumor models
- Quality assurance according to DIN EN ISO 9001:2015
- Experimental imaging and image analysis
- Tumor tissue-specific peptides
- Epitope mapping in patient sera

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**Rostock, Mecklenburg-Western Pomerania, Germany**

## Department of Extracorporeal Therapy Systems

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The Department of Extracorporeal Therapy Systems focuses on the development and evaluation of extracorporeal (outside the body), organ-supporting 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.

### Core competencies

- Cellular biosensors
- Medical devices for blood purification
- Dialysis procedure
- Organ-supporting technologies

## 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.

### Core competencies

- Medicinal chemistry
- Assay and model development
- Neurodegenerative diseases
- Pharmacology
- Drug development
- Drug design (in silico)
- Drug testing (preclinical)
- Synthesis



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## 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 (CCCrho), which serves as a resource for developing production processes for novel, industrial bioproducts.

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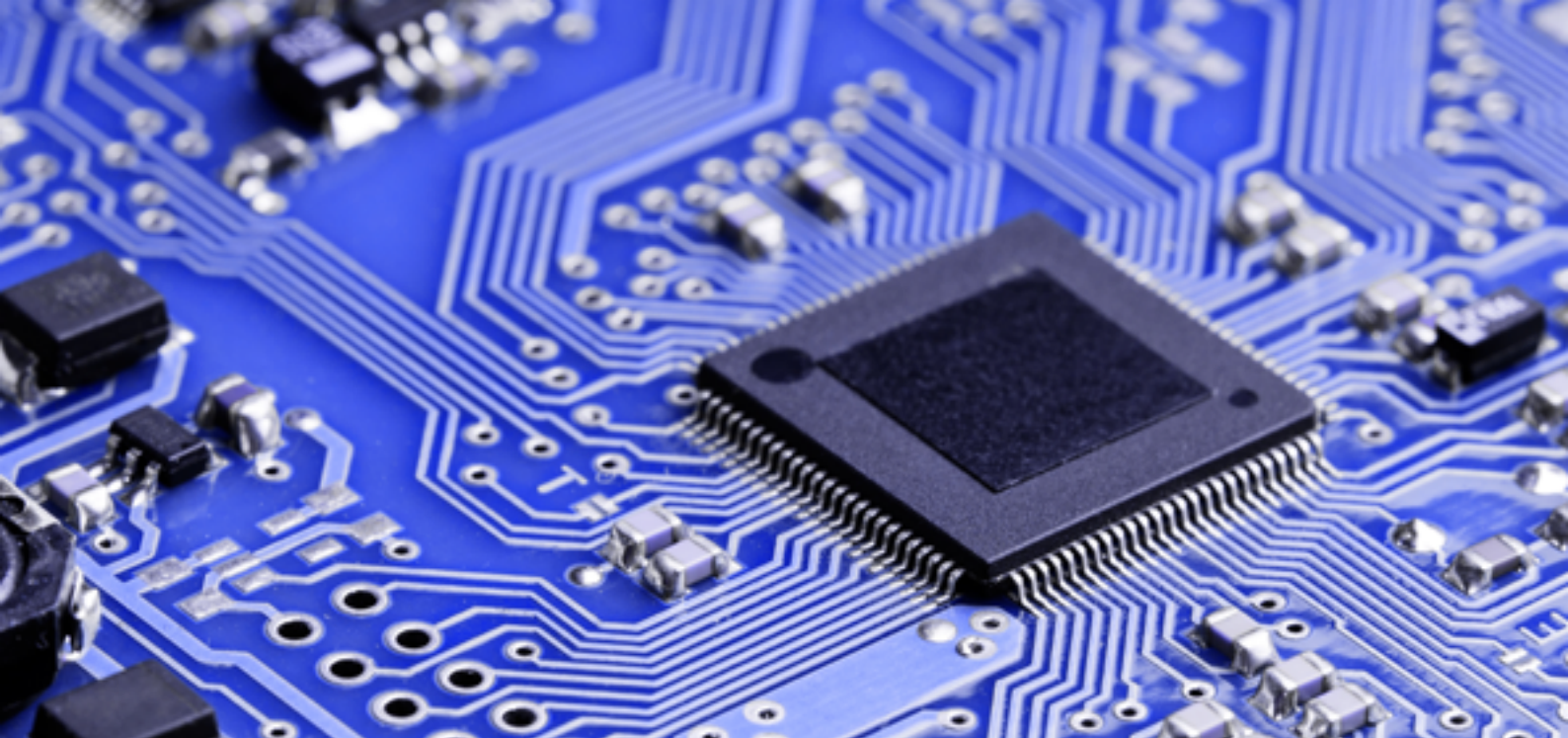
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**Erfurt, Thuringia, Germany**

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## 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.

**[www.meos.fraunhofer.de/en](http://www.meos.fraunhofer.de/en)**

### **Involved Fraunhofer institutes**

Fraunhofer Institute for Applied Optics and Precision Engineering IOF

**[www.iof.fraunhofer.de/en](http://www.iof.fraunhofer.de/en)**

Fraunhofer Institute for Photonic Microsystems IPMS

**[www.ipms.fraunhofer.de/en](http://www.ipms.fraunhofer.de/en)**

Fraunhofer Institute for Cell Therapy and Immunology IZI

**[www.izi.fraunhofer.de/en](http://www.izi.fraunhofer.de/en)**

### **Contact at Fraunhofer IZI**

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# Central facilities

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## GLP test facility

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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 for testing category 9 since 2009. Among other things, this includes safety tests for ATMP immunotoxicity / immunogenicity, biodistribution and tumorigenicity in vitro and in vivo. Testing category 2 was added to the portfolio in 2023, which includes tests to determine toxicological properties.

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.



# GMP manufacturing



## Why are GMP and GLP important?

A clinical trial of a new drug candidate 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 trial. 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.

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.

## Advanced Therapy Medicinal Products (ATMPs)

The Fraunhofer IZI maintains two GMP-compliant clean room facilities for the manufacturing of 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. Through the flexible design, the facilities are especially attractive for companies that seek to bring newly developed

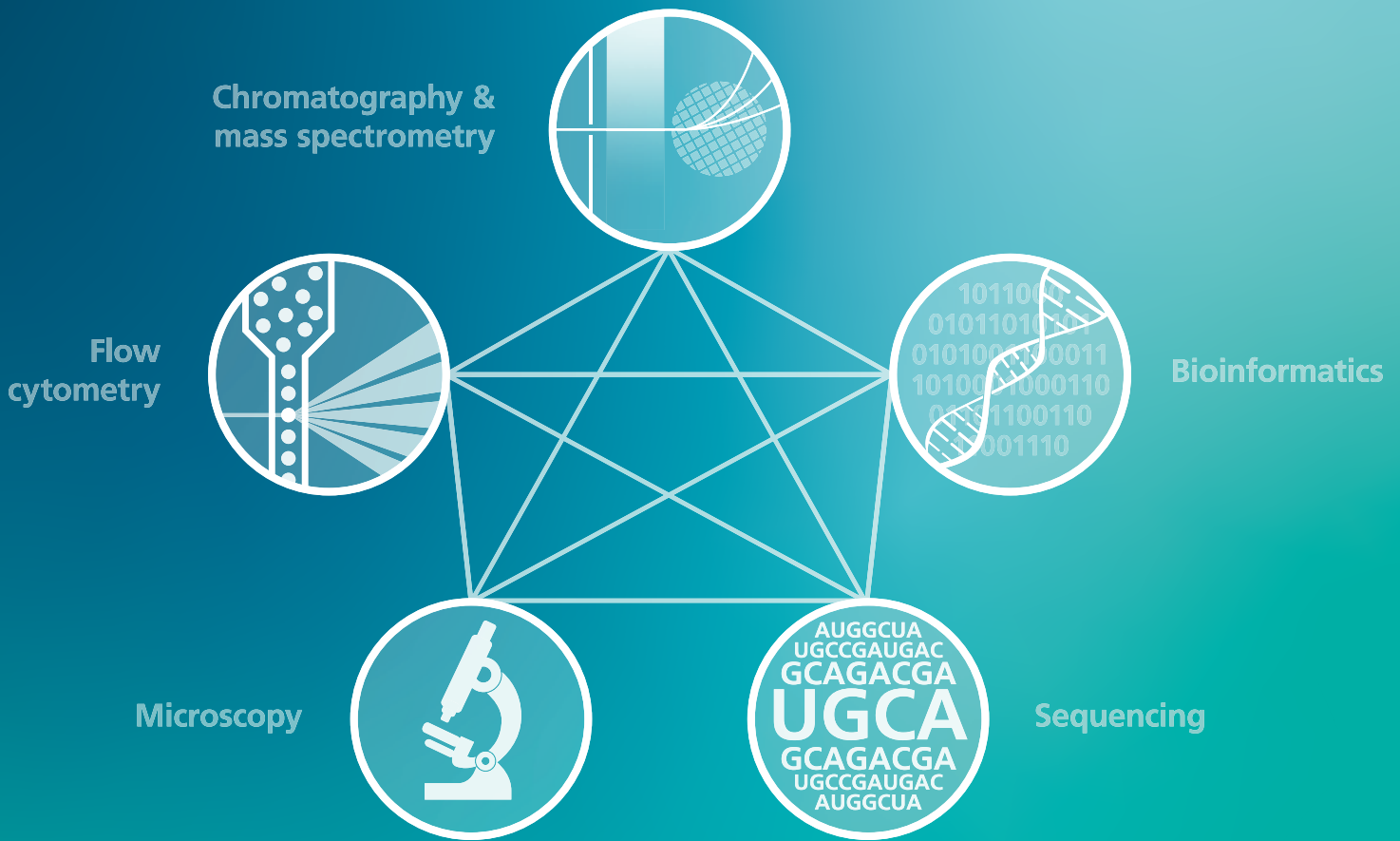
medicinal products into clinical application via clinical trials. The facilities are divided into different independent suites. Each has its own grade C clean room (preparation), own air locks from grade C to B (personnel and materials transfer) and two grade B rooms (aseptic manufacturing). The clean 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).

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## Advanced Analytics Technology Platform

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The Advanced Analytics technology platform bundles existing analytical competencies and technologies for data evaluation and interpretation at Fraunhofer IZI.

With a broad portfolio of state-of-the-art technologies and corresponding expertise, customers and partners are supported with comprehensive analyses in the development of a wide range of therapeutics and diagnostics.

Assays can be developed at different scales or complete proof-of-concept studies can be realized according to customer-specific requirements. The platform's subdivisions work together in an integrative manner, from study design and experiment execution to multi-modal data evaluation.

The Advanced Analytics technology platform bundles the following competencies:

## Chromatography and mass spectrometry

- Preparative chromatographic separations (RP, SEC, IC) Identity determination of isolated proteins by peptide mass fingerprinting (PMF) and MS/MS analyses
- MS-based elucidation and detection of protein modifications and protein interactions
- Consulting, sample preparation, performance and evaluation of proteomics studies
- Determination of toxins and metabolites in biofluids by Multiple Reaction Monitoring (MRM)
- Analysis of active substances and their degradation products by MRM
- Characterization of ssDNA and ssDNA conjugates

## Flow cytometry and FACS

- Cell-based assays (immunophenotyping, apoptosis, internalization, proliferation / cell cycle, migration, degranulation)
- Bacteria-binding assay
- Cell sorting

## Microscopy / Imaging

- Multimodal imaging for preclinical research
- Brightfield, live cell, fluorescence and confocal laser scanning microscopy
- Slide scanning services
- In vivo imaging via magnetic resonance imaging (MRI), computed tomography (CT) and optical imaging (BLI / FLI) for small animals
- Evaluation of various (also correlative) image data
- Microscopy training of users and technical support

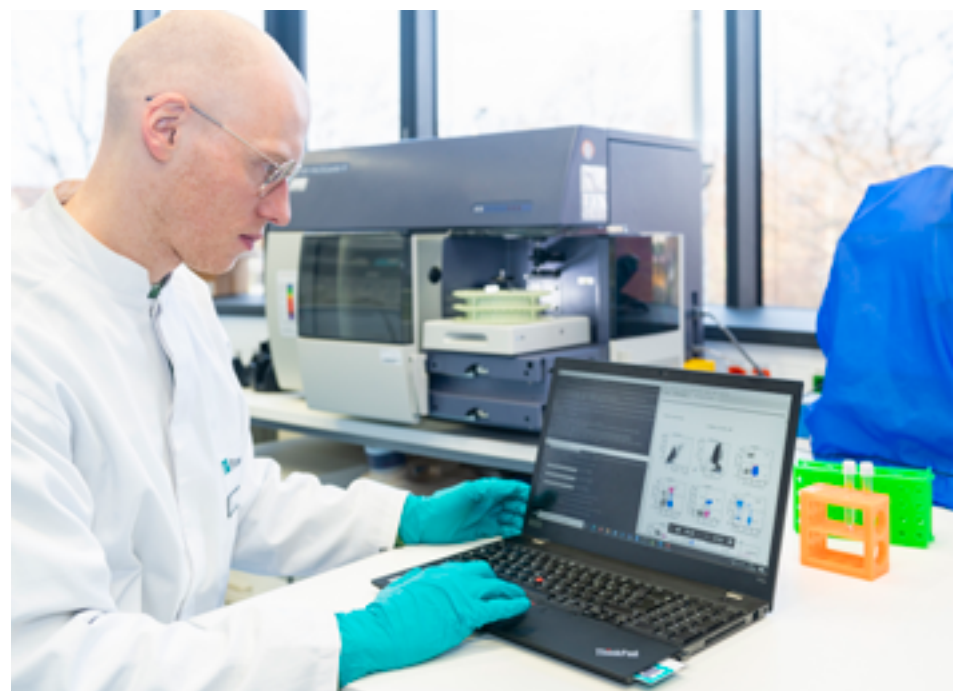
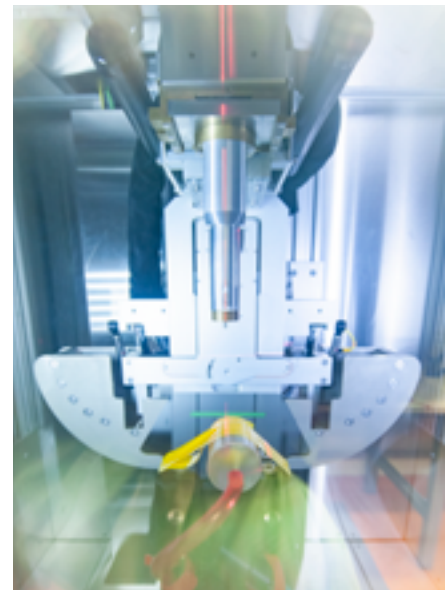
## Sequencing

- Classical next generation sequencing (NGS) methods
  - Whole transcriptome sequencing (mRNA and total RNA)
  - Whole genome and exome sequencing
  - Small genome and 16S sequencing
- Advanced NGS methods
  - Single-cell multi-omics
  - Spatial transcriptomics



## Bioinformatics and machine learning

- Machine learning & multi-omics: Machine learning & AI for deep molecular data; multi-modal data science; statistical learning; integrative bioinformatics; pipeline development
- Software components for IVDs: Development of algorithms and software components for medical devices in particular in vitro diagnostic devices (IVDs) and lab developed tests



## 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.

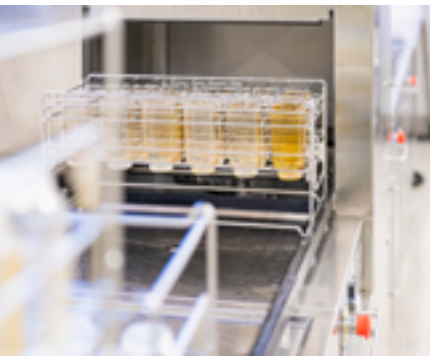
All experimental work can be carried out under practically sterile conditions. Several fully fitted operating suites allow small and large animals to be examined and treated. The comprehensive, state-of-the-art equipment guarantees correct anesthesia, analgesia and species-relevant blood analyses.

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



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).

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.

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

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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 1500 m<sup>3</sup>/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, a climate cabinet 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 (TCID<sub>50</sub>, 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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Fraun



## Selected projects

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## Immuno-oncology

# Cell adapters pave the way for affordable cancer immunotherapy

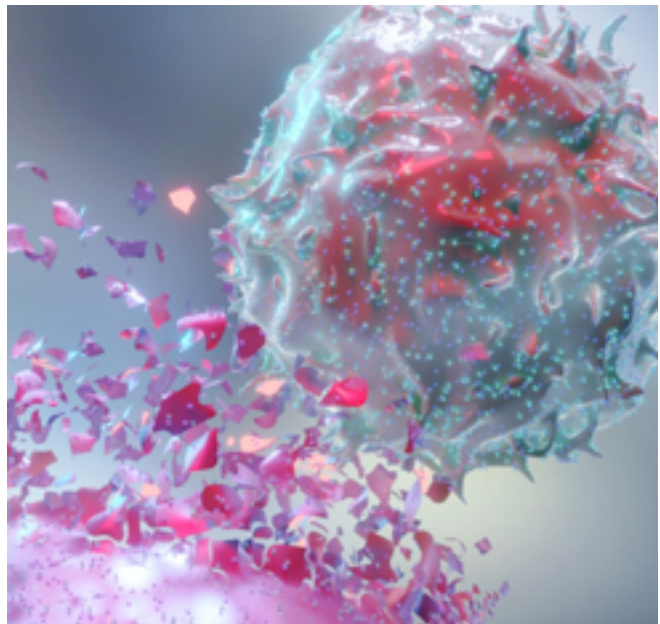
The approvals granted for the first CAR (chimeric antigen receptor) T cell therapies have expanded the treatment options for various types of leukemia and lymphomas.

Alongside the optimization and automation of therapeutic procedures, the development of off-the-shelf products based on cells from the innate immune system, such as macrophages and natural killer (NK) cells, is increasingly shifting into the focus of research and development approaches.

One such approach is the manufacture of CAR-modified NK cells from healthy donors (CAR-NK cells). These are emerging as a promising cell resource that can be manufactured and stored independently of the patient. This approach would significantly increase the availability of these therapeutic agents with regard to both time and quantity.

A further approach is being pursued by Heidelberg-based Affimed GmbH. The immuno-oncology company is developing bispecific antibodies, known as Innate Cell Engagers (ICE®), which act as adapters and establish a connection between cells from the innate immune system (e.g. NK cells) and tumor cells. The ICE® recognize CD16A on the NK cell on the one hand and a tumor antigen on the tumor cell on the other, bringing the NK and the tumor cell together. Within this complex, the NK cell is activated and kills the tumor cell.

As part of a proof-of-concept study, the two approaches (CAR-NK and NK plus ICE®) will be evaluated at Fraunhofer IZI in cooperation with Affimed. NK cells from healthy donors will be isolated and modified to become CAR-NK cells designed to



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target a specific tumor antigen. Alongside this, NK cells will be incubated with a bispecific ICE®. The two cell preparations will subsequently be brought together with tumor-antigen-positive tumor cells before being screened and compared in vitro for their phenotypic and cytotoxic properties. Moreover, the efficiency and the efficacy profiles of both approaches are to be evaluated in tumor xenograft models in the mouse.

The cooperation between Fraunhofer IZI and Affimed GmbH is expected to provide valuable insights into the mechanism of action and effectiveness of the approaches of both the CAR-NK cells and the ICE® combination, which can then be harnessed when developing the therapies against various cancer indications.

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## Immuno-oncology

# T-Charge™ – optimizing CAR-T cell technology



After successfully establishing routine manufacture at Novartis' manufacturing facilities, the continued collaboration will now focus on manufacturing novel next-generation CAR-T investigational drugs developed by Novartis. A key feature of the T-Charge™ platform is the preservation and / or improvement of T cell stemness, i.e. the T cells' ability to self-renew and mature. This leads to a product with a greater proliferative potential and fewer exhausted T cells, which is likely closely connected to its therapeutic potential.

With T-Charge™, CAR-T cell expansion occurs primarily in the patient's body (in vivo), eliminating the need for an extended culture time outside of the body (ex vivo). In addition to the altered cell properties, the T-Charge™ products will therefore be more readily available to patients compared with the conventional CAR-T technology due to their simplified processes and optimized quality control. Not only patients, but also the health-care system as a whole would benefit from this.

### Partners

Novartis

CAR-T cell therapy is a type of cancer immunotherapy. It uses the patient's own T cells to fight certain types of cancer. In order to do this, the cells are collected in the clinic by leukapheresis before being genetically reprogrammed in vitro in such a way that they can use a chimeric antigen receptor to recognize cancer cells that have a special antigen on the cell surface. Following lymphodepleting chemotherapy, the reprogrammed cells are administered to the patient by way of infusion, where they are able to proliferate and trigger the immune response.

Fraunhofer IZI has been assisting and supporting the company Novartis since as early as 2015 with the manufacture and further development of the CAR-T cell therapy Kymriah® (tisagenlecleucel).

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## Immuno-oncology

# ROR-1 CAR-T cell therapy

Cancer is the second most common cause of death in Germany. For years now, the number of new cancer diagnoses has seen a steady rise. There continues to be an enormous need for new therapeutic options to treat all kinds of cancer. In 2017 and 2018 respectively, the US Food and Drug Administration (FDA) and the European Commission approved the first ever form of cell and gene therapy for the treatment of cancer – CAR-T cell therapy. CAR stands for chimeric antigen receptor, which is expressed through a genetic modification on the T cells. The receptor identifies and binds specific antigens on cancer cells, subsequently activating a targeted immune response.

This revolutionary type of therapy also lies at the heart of the ROR-1 CAR-T research project. ROR-1 is a tyrosine-protein kinase transmembrane receptor, which is strongly expressed during embryonic development, but rarely on healthy adult cells. A high level of ROR-1 expression has been detected on mantle cell lymphoma tumor cells as well as in the case of breast cancer. CAR-T cells designed to target surface molecule ROR-1 are to be used to address hematological tumors such as mantle cell lymphoma but also solid tumors such as breast and lung cancer.

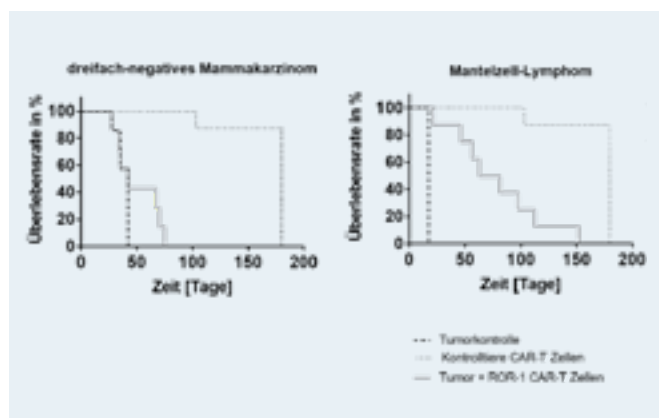
In order to manufacture this kind of therapeutic agent, immune cells are taken from the patient's body by means of leukapheresis. T helper cells and cytotoxic T cells are then selected by magnetic cell separation. The genetic material for

the CAR is introduced into the genome of the T cells via a non-viral gene transfer using the "Sleeping Beauty" transposon system (jumping gene). This reprograms the T cells in such a way that they perceive ROR-1-positive cancer cells as "foreign" and eliminate them by releasing cytotoxic messengers. The reprogrammed cells are multiplied and administered to the patient intravenously.

The project is being funded as a pilot project under the proof-of-concept initiative launched by the Fraunhofer-Gesellschaft, the Helmholtz Association and Deutsche Hochschulmedizin in order to promote the translation of innovative research projects. With the help of this funding, preclinical trials investigating the safety and efficacy of the ROR-1 CAR-T cells have been conducted at Fraunhofer IZI and the pharmaceutical manufacture of the therapeutic agent has been established, with the aim of achieving clinical translation in a phase I / II study (first in man).

The preclinical GLP studies conducted to verify safety and efficacy are a must in meeting the necessary requirements to begin clinical testing. In the pilot study, the survival, tumor growth and persistence of the CAR-T cells were investigated in an appropriate in vivo model (mouse). Besides this, macroscopic dissection findings as well as serum analyses and histological examinations were performed. It could be demonstrated here that the ROR-1-targeted CAR-T cell therapy shows a survival benefit in the case of mantle cell lymphoma,

*Kaplan-Meier survival curves of xenograft NSG mice with triple-negative breast cancer and mantle cell lymphoma, and of the tumor control group and the ROR-1 CAR-T control group.*



but not in the case of triple-negative breast cancer. None of the further analyses such as serological or histological analyses of the main organs showed any pathological effects.

Test batches were produced in the project to begin with; these batches were used to optimize the process in line with the stringent production requirements under GMP conditions and to qualify the necessary equipment. After successfully establishing the process and determining the required specifications, three successful validation batches were produced in the clean room and the analytical methods were established.

Using the cell products generated in these validation batches, the analytical methods relevant to microbiological safety (mycoplasmas, sterility, bacterial endotoxins) and the verification of genomic safety (determining the vector copy number) were also validated. Finally, a product stability test was performed, which culminated in the successful realization

of an additional batch. Once the validations were complete, an application was made to and granted by the competent authority to include the investigational medicinal product in the existing manufacturing authorization pursuant to Section 13 of the German Medicinal Products Act (AMG).

#### Partners

Max Delbrück Center for Molecular Medicine; University Hospital Würzburg, Department of Internal Medicine II



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## Immuno-oncology | infectious disease pathology

# Automated production technologies for mRNA-based drugs



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mRNA-based vaccines, along with gene and cell therapeutics, represent innovative drugs that can be used to prevent or treat infectious diseases, genetic disorders and cancer. Development of these drugs has been prodigious in recent years in terms of clinical research, translation and application. But advancement of the required production technologies has not yet managed to keep pace with the rapid biomedical progress made in these areas. Hence the need for automated and digitally supported production technologies that facilitate not only the rapid, safe and reliable development of mRNA-based drugs, but also their production in accordance with the high demands of pharmaceutical manufacturing.

The RNAuto lighthouse project focuses on developing bioprocessing methods and production technologies for the modular and automated manufacture of mRNAs, mRNA nanocarriers and mRNA-modified cells that can be scaled right up to industry level. For the automated manufacture of corresponding products to be successful, technical solutions will be developed in the areas of bioreactors, fluid dynamics, quality control and automated data analysis. Core elements of the Industry 4.0 concept are to be deployed to digitally map and monitor the production processes.

The primary objective is to develop automated manufacturing processes for mRNA molecules that will smooth the way for sustainable and cost-efficient health care. To this end, the project brings together the expertise of various Fraunhofer institutes from the fields of vaccine development, cell and gene therapy, bioprocess development, smart sensor technology, and the automation and digitalization of production processes.

Fraunhofer IZI is contributing its expertise in the development of innovative vaccine technologies and cell-based immune therapeutics. Alongside the development of GMP-compliant manufacturing processes, the project will also benefit from the institute's competences in the field of molecular drug design and the preclinical testing of novel drug candidates.

### Partners

Fraunhofer Institute for Toxicology and Experimental Medicine ITEM; Fraunhofer Institute for Microengineering and Microsystems IMM; Fraunhofer Institute for Manufacturing Engineering and Automation IPA; Fraunhofer Institute for Production Technology IPT; Fraunhofer Institute for Experimental Software Engineering IESE; Fraunhofer Institute for Microelectronic Circuits and Systems IMS

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## Infectious disease pathology

# Antibiotic-free: Toxin adsorbers for the treatment of gastrointestinal infectious diseases

After receiving systemic antibiotic therapies, patients experience a loss of or reduction in healthy gut microbiota. This often leads to an infection caused by pathogenic bacterial strains such as *Clostridioides difficile*. Toxins released by the pathogens impede restoration of the gut microbiome and lead to the manifestation of disease symptoms such as severe diarrhea. Treating a *Clostridioides difficile* infection has always necessitated the use of additional antibiotics. However, this type of therapy does not address disease-relevant toxins. This is in spite of the fact that their adsorption from the intestinal tract would in fact have an immediate positive impact on clinical symptoms and would accelerate repopulation with commensal species.

With this in mind, researchers at Fraunhofer IZI are developing adsorbent materials that can be used to bind the harmful toxins and remove them from the body. Together with industry partner AdFiS products GmbH, a large number of different toxin adsorbers were examined with an eye to their adsorption capacities.

In doing this, a potent activated carbon with good adsorption properties was able to be identified for various *Clostridioides difficile* toxins as well as toxins from other infection-relevant pathogens (*E. Coli* and *S. aureus*). It could be demonstrated in cell cultures that these activated carbons bind up to 85 percent of the bacterial toxins, depending on the concentration. In a specially developed model of the gut, in which different physiological influencing factors were reproduced, binding capacity still reached up to 70 percent.

The foundations for the future development of an oral medical device were thus able to be created in this project, which can be used to reduce or even replace antibiotics in the treatment of gastrointestinal infectious diseases.

### Partners

AdFiS products GmbH



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## Infectious disease pathology

# Safe travels – evaluation of germ reduction methods in aircraft

The coronavirus pandemic has once again highlighted just how quickly and extensively pathogenic germs can spread around the globe.

Alongside medical prevention and treatment strategies, methods and technologies are also required that reduce the survival rate and time of germs outside of the body and limit transmission routes.



Particularly critical areas here include public infrastructures as well as transport and traffic systems. On behalf of the company Airbus, Fraunhofer IZI is evaluating various physical and chemical disinfection methods for reducing the viral load in aircraft cabins.

Tests were conducted in the S3 safety laboratory at Fraunhofer IZI, initially using cell-culture-based test systems, to see how effectively the methods in question are able to inactivate SARS-CoV-2 on a range of surfaces. The tests were performed in a climatic test cabinet, where different temperatures and relative humidity levels can be defined and set, in order to examine different climatic effects (e.g. the dry air in an aircraft, or the warm and humid air in tropical countries).

Using what are known as surrogate viruses, i.e. similar but harmless types of virus, practical tests were then conducted in a replica aircraft cabin before being evaluated in the laboratory. Further investigations will assess the suitability of special surface coatings in reducing germ load.

The results will help optimize cleaning and disinfection methods and will influence the future selection of materials for new models.

### Partners

Airbus

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## Infectious disease pathology

# FLAVICURE – antiviral agents to combat West Nile and Zika viruses



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Due to the effects of climate change, the average winter in Central and Northern Europe is becoming increasingly mild. This is causing insect species and, in turn, pathogens that just a few years ago had been endemic exclusively to warmer regions to spread further afield. These include, for example, West Nile and Zika virus from the flavivirus genus. These pathogens are transmitted to mammals and humans by mosquitoes and can sometimes cause severe illnesses. Sufficient treatment options are yet to be found; the only preventive strategy is to avoid mosquito bites.

As part of the FLAVICURE project, an antiviral agent with broad-ranging efficacy is to be developed for the first time to treat infections caused by West Nile and Zika viruses. Together with project partners Protinhi Therapeutics (Nijmegen, Netherlands) and Chimera Biotec GmbH (Dortmund), Fraunhofer IZI is working on the development of suitable drug candidates.

In the S3 safety laboratory at Fraunhofer IZI, a number of substances were tested in cell cultures for their efficacy and the optimal concentration for inhibiting the viruses was determined. The substances that showed potential for further development could thus be identified with the help of dose-response curves. The efficacy and safety of the potential drug candidates will now be evaluated further in the next stage using suitable animal models. Based on these results, the most promising candidate is to then be selected and prepared for clinical development.

### Partners

Protinhi Therapeutics (Nijmegen, The Netherlands); Chimera Biotec GmbH (Dortmund, Germany)



*The project is being funded as part of the Eurostars program, a funding program open to all fields for small and medium-sized companies that carry out research and development projects under the EUREKA European research initiative together with partners from other member states ([www.eurostars-eureka.eu](http://www.eurostars-eureka.eu)).*

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## Infectious disease pathology

# Non-invasive diagnostics for detecting infections in respiratory air

In a recent special report, the World Health Organization pointedly describes why the fight against antibiotic resistance is one of the largest tasks facing the global community. By 2050, the organization expects to see 10 million deaths annually caused by infecting agents [1]. Innovations are necessary not only with an eye to treatment, but also in order to detect and diagnose the pathogens that cause the underlying diseases and, ultimately, to counteract the health-care challenge.

To improve this situation, the BreathAlert project, launched at the end of 2020, aims to develop a new method for the quick and non-invasive detection of infecting agents and existing antibiotic resistances, which analyzes patients' respiratory air. The project focuses on the continued advancement of gas chromatography–ion mobility spectrometry, which is intended to be used to characterize volatile organic compounds (VOCs) from microorganisms.

Investigations were carried out on select microorganisms at Fraunhofer IZI to see whether they can be distinguished via emitted VOCs and assigned to the respective bacterial species. To do this, the pathogens were first cultivated before the headspace, i.e. the gas space above the culture medium, was guided into the device. The VOCs were ionized, separated in the electric field, and then detected at staggered time intervals. A software-assisted evaluation workflow was used to analyze the complex data. The focus was placed here on bacterial species *E. coli* and *S. aureus*, whose increasing resistances were categorized as concerning by the WHO [1]. Using the applied methods, specific VOC profiles could be identified which are



*One exhaled breath and four minutes' time are all it takes to determine whether someone is healthy or suffering from COVID-19 or a different type of cold.*

able to reliably differentiate between bacteria, even under different conditions. Notable here was that even the individual antibiotic-resistant strains were able to be made out.

Clinical swab specimens and respiratory air samples taken from infected patients will continue to be investigated until the end of the project. Tests will also be conducted as to whether or not the methods previously developed in the laboratory can also be applied to humans. In further studies involving hospitals and a family practice, the project partners were already able to show, using the method, that the exhaled VOC profiles from COVID-19 patients, patients suffering from other types of cold and healthy subjects did in fact differ from one another. One exhaled breath is all it takes to obtain a result within four minutes.

The company Graupner medical solutions GmbH is developing the medical device technology as a consortium partner and will commercially exploit the results. The development activities will be supported by specialized clinics, which enable access to samples and will carry out a final validation.

### Partners

Graupner medical solutions GmbH

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*[1] World Health Organization Report 2017: Prioritization of Pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. WHO/EMPI/IAUI/2017.12.*

## Infectious disease pathology

# Development of therapeutic antibodies for HERV-associated autoimmune and tumor diseases

Human endogenous retroviruses (HERVs) and, more specifically, their envelope proteins are suspected of transporting diseases such as multiple sclerosis, rheumatism and tumor diseases. The actual function of these specific factors is yet to be clarified. Cellular damage and the misdirected stimulation of the immune system caused by HERVs are presumed to be disease mechanisms. New findings should help shed light on the role played by HERVs in the emergence of autoimmune and tumor diseases.

As part of a joint research project with Halle University Hospital, researchers at Fraunhofer IZI were able to manufacture HERV envelope proteins using biotechnological methods and characterize their biological activity. These proteins also served as antigens for generating both polyclonal and monoclonal antibodies. Furthermore, the biological effects of HERV envelope proteins were able to be examined in cell cultures and experimental animals, and their immune-stimulatory properties characterized. Together with the project

partners from Halle University Hospital, HERV sequences could also be identified in various tumor entities.

The research project is thus paving the way for new therapeutic procedures in the treatment of autoimmune and tumor diseases.

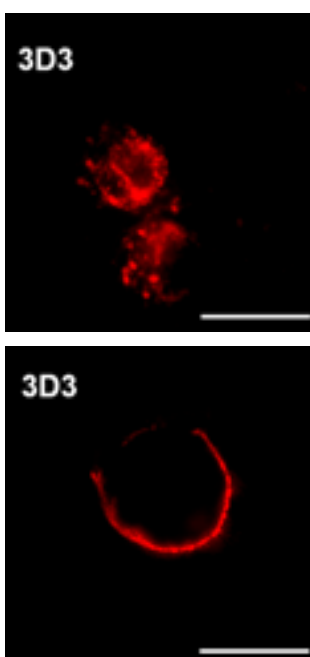
The project "Characterization of HERV envelope proteins aimed at developing therapeutic antibodies for HERV-associated autoimmune and tumor diseases" was funded by the European Regional Development Fund (ERDF) and the State of Saxony-Anhalt. The funding was awarded as part of the "Saxony-Anhalt SCIENCE – FOCUS" program, through which the State of Saxony-Anhalt supports specialist research activities and innovative research projects in the field of science.

### Publications

<https://www.mdpi.com/1422-0067/23/15/8330>  
<https://www.mdpi.com/1424-8247/14/1/70>

### Partners

Medical Faculty of the Martin-Luther-University  
Halle-Wittenberg



*Fluorescence microscopy images of transfected HEK293F cells with the HERV-Fc1 Env-specific antibody 3D3 (red) show the occurrence of the envelope protein inside the cell in the case of permeabilized cells (above) and on the cell surface in the case of cells with an intact cell membrane.*



SACHSEN-ANHALT



EUROPÄISCHE UNION  
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## Infectious disease pathology

# Selective active agents and application systems for the treatment of bacterial infectious diseases affecting the periodontium

Periodontitis, commonly referred to as gum disease, is an inflammatory disease of the periodontium that affects almost every second adult in Germany. It is caused by a local infection involving specific oral microorganisms and the subsequent local immune response. Left untreated, periodontitis leads to tooth loss and bone loss in the jaw. Studies also show that chronic periodontitis drastically increases the risk of developing diabetes, cardiovascular diseases and rheumatoid arthritis.

All of the preparations used to date come with the major drawback that their active agent is a broad-spectrum antibiotic and / or antiseptic. This means they kill all the bacteria found in dental plaque, including desired commensal bacteria in the oral microbiome, which often leads to the treated areas being recolonized by the germs that cause the disease.

Together with Periotrap Pharmaceuticals GmbH, the Fraunhofer Institute for Microstructure of Materials and Systems IMWS and Martin Luther University of Halle-Wittenberg, researchers at Fraunhofer IZI developed a pathogen-specific form of therapy. This is based on an agent that acts selectively to severely diminish the pathogenicity of the bacteria that cause periodontitis by inhibiting an essential enzyme: bacterial glutaminy cyclase. The Fraunhofer IZI researchers primarily examined pharmacokinetic properties such as potential absorption of the active agent into the organism. Besides this, investigations were conducted into the stability and release of drug candidates from controlled release drug delivery systems. Extremely precise and sensitive



*The stability and release of drug candidates was investigated using techniques such as mass spectrometry.*

mass spectrometry is employed in particular here, which enables even the lowest concentrations of an active agent to be measured in an organism. Research has also been conducted into a suitable route of administration that is as straightforward and pain-free as possible, and initial model systems have been tested. Maintaining the concentration of the agent at the target location presents a particular challenge as active agents are usually washed out quickly in the mouth and especially around the gum pockets due to mechanical influences and the constant flow of liquid. Once the research project is complete, Periotrap Pharmaceuticals GmbH will continue to work on preparing the therapeutic approach for the market.

The project "Controlled release drug delivery systems of innovative and selective drug molecules for the treatment of bacterial infectious diseases of the periodontium (ParoStop)" was supported by the Land of Saxony-Anhalt using funds provided by the European Regional Development Fund (ERDF).

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SACHSEN-ANHALT



EUROPÄISCHE UNION  
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Europäischer Fonds für  
regionale Entwicklung

### Partners

Periotrap Pharmaceuticals GmbH; Fraunhofer Institute for Microstructure of Materials and Systems IMWS; Martin-Luther-University Halle-Wittenberg

## Infectious disease pathology

# Drug Repurposing



It takes a lot of time and money to develop new drugs. Drug candidates are identified for a particular indication based on findings from foundational research, which can take decades to evolve. These are first examined in great detail as to their efficacy and, above all, safety in various cell culture and animal models during the preclinical development phase. Only the few drug candidates whose benefit-risk profile justify being tested on human subjects make it into clinical development, where they are tested first on healthy subjects (phase I), then in smaller patient cohorts (phase II) and finally in trials involving as many patients as possible (phase III) before an application can be made for approval in the indication concerned.

In the case of drug repurposing, medicines which are already approved are tested for their suitability and possible applications in other indications. A prerequisite here is a thorough understanding of the disease mechanisms at a molecular and cellular level on the one hand and the precise characterization of the medicine's principles of action on the other. If corresponding parallels are identified in different indications, it is worth taking development steps to expand the medicine's area of application. This approach to medicine development is extremely efficient and takes much less time and effort as it can build on existing data and observations.

The REMEDI4ALL project plans to develop a Europe-wide competence platform to support European research institutes with drug repurposing in the future.

Fraunhofer IZI is contributing its competences in infection research to the consortium and will investigate the suitability of a previously approved oncology medicine for its application in the case of COVID-19 diseases.

The REMEDI4ALL consortium comprises 24 partners and will be supported over a number of years with funding in the value of 23 million euros from the European Union's Horizon Europe research and innovation program under grant agreement ID 101057442.

<https://remedi4all.org>

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## Infectious disease pathology

# Preclinical GLP study to assess the immunotoxicity of a therapeutic HBV vaccine (TherVacB)

Hepatitis B is one of the most common forms of viral liver inflammation in the world. Infection can be chronic, possibly leading to liver cirrhosis and hepatic cancer. At the German Center for Infection Research (DZIF), a consortium made up of 35 German research institutes, new treatment options are being investigated for patients diagnosed with chronic hepatitis B. Within this consortium, researchers from Helmholtz Center München and the Technical University of Munich developed the therapeutic hepatitis B vaccine TherVacB.

As part of the proof-of-concept initiative, Fraunhofer IZI conducted a preclinical trial in its GLP test facility to examine the safety of this adjuvanted vaccine. A mouse model that imitates the condition of someone diagnosed with chronic hepatitis was used to assess immunotoxic effects on the one hand and confirm the efficacy of the TherVacB vaccine on the other. Moreover, any potential, toxic side effects of the individual vaccine components (HBV peptides, adjuvants, MVA vectors) were also to be assessed.

It could be demonstrated that the vaccine candidates bring about the necessary activation of B cells. Besides this, antibodies were detected that are directed against the membrane protein on the cell surface of the hepatitis B virus. A clear response specific to the hepatitis B virus was also measurable among the relevant T cells. The hematological and clinical-chemical parameters were within the normal range and the pathohistological examinations showed predominantly

low-grade changes in the liver as is to be expected with an immune response. Inflammatory lesions in the liver are depicted in the figure as an example. The preclinical trials conducted at Fraunhofer IZI are a prerequisite for the planned clinical trials.

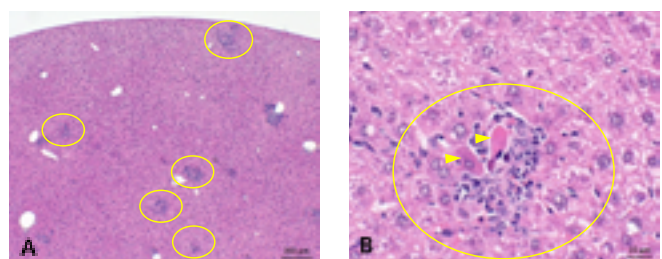
The proof-of-concept initiative was set in motion by the Deutsche Hochschulmedizin, the Fraunhofer-Gesellschaft and the Helmholtz Association in order to accelerate the translation process from highly innovative approaches anchored in foundational research into medical practice.

### Partners

Helmholtz Munich; Medical Center Hamburg-Eppendorf (UKE); University Hospital rechts der Isar of the Technical University Munich (TUM)

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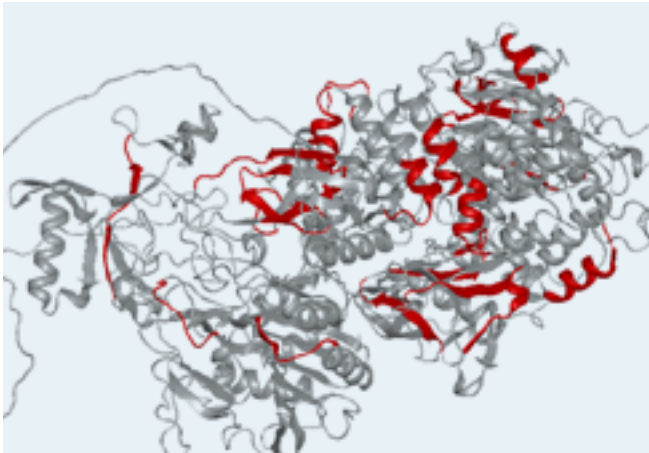


*Examples of focal inflammation in the hepatic tissue of a mouse that was vaccinated as part of the trial. A: Overview magnification of a HE-stained liver section featuring several small and medium-sized inflammatory foci (ellipses) | B: Magnified depiction of an intralobular, medium-sized focus of inflammation (ellipsis) from image A with intralobular apoptotic hepatocyte cell fragments (arrowheads).*



## Infectious disease pathology

# Development of glycosylated vaccine proteins



*Position of the epitopes (red) in a model of the E.coli YghJ protein, which was able to be validated using peptide arrays.*

Uropathogenic E. coli strains often cause serious urinary tract infections, especially in patients admitted to hospital for the treatment of other diseases. Besides the added strain on patient health, this also gives rise to substantial additional treatment and follow-up costs.

The aim of this project is to develop a vaccine that strengthens the immune response to urinary tract infections, especially in hospital patients. The idea here is for the immune response to specifically target the bacterial protein YghJ, which is essential for the colonization of the urinary tract.

Researchers from the Danish company GlyProVac LLC. have discovered that bacteria such as E. coli modify a large proportion of their proteins using sugar molecules (glycosylation). These modifications have a significant bearing on the immune response and are therefore also of relevance to the development of protective vaccines. GlyProVac LLC. has developed ways of verifying and analyzing these modifications. As part of the project, special host strains will now be developed to manufacture recombinant proteins that are very similar to the naturally occurring YghJ protein but induce an enhanced immune response.

In order to study the immune response to glycosylated and non-glycosylated YghJ vaccine proteins in detail and compare it with the immune response to the natural antigen, the antibodies produced by the immune system must be precisely analyzed. The methods available to date, however, have proven inadequate here.

Researchers from Fraunhofer IZI and epitopic GmbH have thus developed a procedure for the quick and precise identification and analysis of epitopes, i.e. the molecular structures which are recognized and bound by antibodies. Using the procedure, more than 20 epitopes of the YghJ protein were able to be identified and can be drawn upon when evaluating the vaccine candidates (see figure). Further improving the methods should also allow structures to be found that target glycosylation itself.

Comparisons between the animal model and patient serums could already confirm that the developed vaccine candidates trigger an immune response that resembles the natural reaction. The verification procedures developed within the scope of this project will also bear significance for future clinical development.

### Partners

GlyProVac LLC.; epitopic GmbH; Odense University Hospital; Klinikum St. Georg Leipzig



This project has received funding from the Eurostars-2 joint programme with co-funding from the European Union Horizon 2020 research and innovation programme



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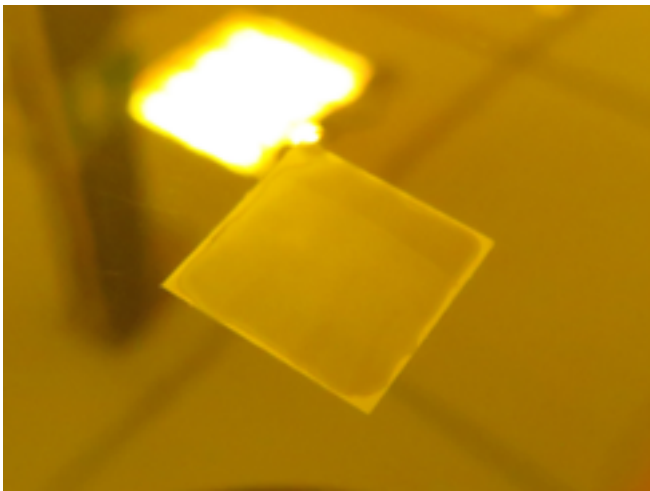
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## Infectious disease pathology

# Biosensors for the detection of infecting agents



*Embedded measuring chip with a BDD (boron-doped diamond) surface. © Fraunhofer IZM*

The corona pandemic made clear just how important it is to have robust technologies in place for the rapid and accurate analysis of disease agents and antibodies in order to monitor infection outbreaks and immunity among larger population groups. This project aims to develop an immunodiagnostic technology platform that can be flexibly adapted to dynamic pandemic activity.

Electrodes made from boron-doped diamond (BDD) are key to this development; they are combined with epitopes, i.e. structures that exist in the pathogen and are recognized by the antibody, to create sensitive and efficient biosensors.

The specific detection of SARS-CoV-2 was initially focused on as a demo application. Fraunhofer IZI is using its expertise to help identify and develop peptide-based epitopes here, which will be taken as a basis for developing sensitive and specific detection systems. Epitopes will be utilized that are already available from projects involving hundreds of patient serums. Serums taken from COVID-19 patients infected with omicron were also used in the project. At the same time, with an eye to long COVID, patient serums and data were analyzed for potential epitopes of autoantigens against proteins produced naturally in the body, which are said to play an important role in the development of long COVID.

Following a modular concept, the platform should be flexibly and quickly adaptable to different disease agents or immunologically relevant questions. The project aims to make devices available for point-of-care diagnostics, for quick and cost-efficient monitoring of infectious diseases and for determining the immune status of vaccinated or recovered individuals within just a few weeks of the outbreak of an infection in the future.

### Partners

Fraunhofer USA Center Midwest CMW, Coatings and Diamond Division; Fraunhofer Institute for Reliability and Microintegration IZM

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## Further selected projects

# ASSESS-MED – on the way to becoming an accredited test laboratory for medical devices

For many patients diagnosed with chronic, irreparable kidney disease, dialysis is an important bridging technology that ensures survival up until kidney transplantation. However, it is more commonly becoming the final therapeutic procedure for those affected as there are simply not enough donor organs available for transplantation.

Consisting of several thousand hollow fibers with a semi-permeable membrane, dialyzers lie at the core of dialysis. In order to best adapt the therapy to each patient's individual requirements, the performance parameters (clearance, sieving coefficient and ultrafiltration coefficient) of a dialyzer have to be as precise as possible and comparably quantified.

Fraunhofer IZI's Rostock-based work group has been supporting customers and partners in the testing and characterization of dialyzers for several years now. The department has been working towards accreditation of its test laboratory since 2018. A key milestone was achieved with the introduction of a quality management system in accordance with ISO/IEC 17025. Moreover, through the test laboratory's continuously close involvement in the department's ongoing research projects, the various technical and quality-based processes are constantly being developed and optimized.

In the 2022 reporting year, the application for accreditation was able to be submitted to the German accreditation body.

This focuses primarily on the performance of clearance measurements, which are used to determine key filtering properties of dialyzers. For a range of target molecules (such



as urea, creatinine, phosphate and vitamin B12), clearance describes the cleaning performance of the semi-permeable hollow fiber membranes per unit time. The goal is to be able to carry out testing orders with legally binding deliverables in this field from next year onwards.



*The ASSESS-MED project is being funded using means provided by the European Union, made available through the European Regional Development Fund (ERDF), as well as the Ministry for Economic Affairs, Labor and Health of Mecklenburg-West Pomerania.*

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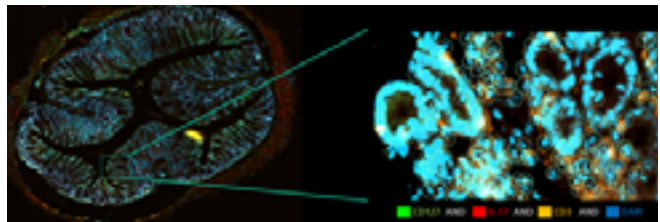


## Further selected projects

# Development of a novel therapeutic concept for chronic inflammatory bowel disease (CIBD) using non-toxic ligands of the aryl hydrocarbon receptor (CIMD\_CED-AhR)

The term chronic inflammatory bowel disease (CIBD) is used to describe disease patterns characterized by intermittent or continuously appearing inflammatory changes to the intestinal epithelium. The two main types of CIBD are Crohn's disease and ulcerative colitis. In Germany, around 300,000 people are affected, enduring complaints that last years such as stomachache, diarrhea, fatigue, eye inflammation, arthritis and psychological impairment. The exact cause of CIBD is unknown. Genetic factors and also environmental influences play a role and induce the destruction of homeostasis at the intestinal epithelial barrier as well as the chronic activation of the local immune system by microbial components. Despite the huge efforts put into developing novel therapeutic approaches to CIBD, only symptomatic rather than causal, curative therapies are currently within sight. More recent studies show that the aryl hydrocarbon receptor (AhR) could offer an approach for a causal therapy.

Aided by repurposing libraries, AhR ligands were therefore identified that have already been classified as safe for other indications in preclinical and clinical trials. Selected candidates were first screened for the induction of anti-inflammatory effects (interleukin(IL)-10 induction, IL-1 $\beta$  suppression) in simple in vitro models using bone marrow macrophages from the mouse. Suitable candidates were then tested in more complex in vitro models (Transwell™ and organoid models based on human enterocytes). The principal testing



*AI-based image evaluation of specific markers in cells taken from the intestinal epithelium in a colitis model (mouse).*

parameters here were the induction of certain tight-junction proteins and cytokine receptors. During this stage of testing, four candidates were identified as promising for further drug development, of which two candidates had already been tested in two different in vivo models (dextran sodium sulfate-induced and bacteria-induced colitis in the mouse). As no significant therapeutic effect could be achieved with either of these two candidates, two additional candidates have since been included in the in vivo testing and one additional candidate has been added to the second in vitro testing stage. The project is being conducted as part of the Fraunhofer Cluster of Excellence Immune-mediated Diseases (CIMD).

### Partners

Fraunhofer Institute for Integrated Circuits IIS; Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Discovery Research ScreeningPort; Fraunhofer Institute for Silicate Research ISC

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## Further selected projects

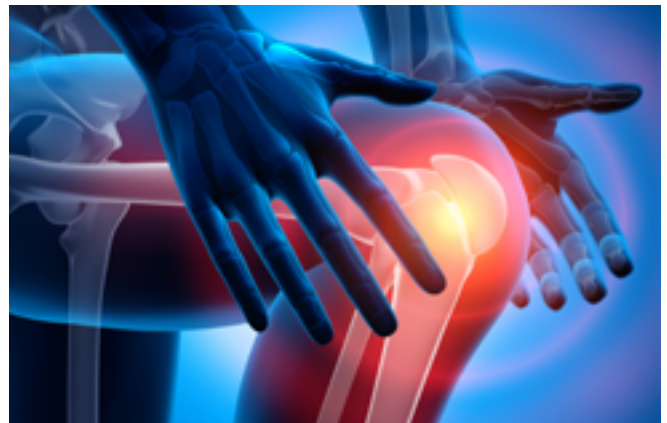
# Validation of manufacturing process and quality controls for a novel cell therapeutic for the treatment of focal cartilage defects in the knee

The aim of this project is to validate a manufacturing process, including safety-relevant quality controls, for a novel, allogeneic cell therapeutic to be used in the treatment of focal cartilage defects in the knee.

Developed by BioPlanta GmbH, the product is based on mesenchymal stem cells derived from the umbilical cord. These types of cells boast an exceptionally high level of immune tolerance, making them suitable for allogeneic therapy concepts. The immunomodulating properties of mesenchymal stem cells have an anti-inflammatory effect, activate regenerative processes, and help restore hyaline cartilage. The project's therapeutic goals are therefore to relieve pain, improve mobility and reduce symptoms of arthrosis in the knee.

The collaboration project will also establish the scientific and technical requirements for the pharmaceutical manufacture of the investigational medicinal product and for dispensing it to patients as part of a clinical trial. The product is to be classified as an advanced therapy medicinal product (ATMP).

In line with both German and European regulations, validation of the manufacturing process and the respective safety-relevant analytical methods (quality controls) are central to verifying the safe, robust and reproducible manufacture of the ATMP. This includes, among other things, testing for sterility and bacterial endotoxins. The aim of the project is to update the assortment list covered by Fraunhofer IZI's existing manufacturing authorization pursuant to Section 13 of the German Medicinal Products Act (AMG).



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The product has already undergone extensive testing under GLP conditions in the GLP test facility at Fraunhofer IZI with regard to potential undesirable biodistribution and tumorigenicity.

### Partners

BioPlanta GmbH

Europa fördert Sachsen.



*The measure is co-financed with tax funds on the basis of the budget approved by the Saxon State Parliament.*

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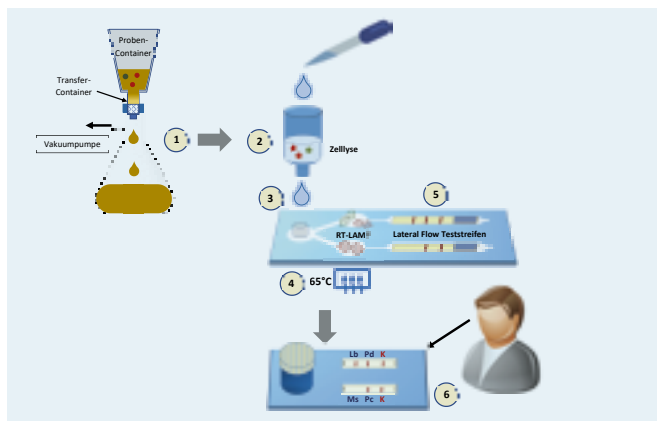
## Further selected projects

# Test platform for the rapid detection of beer-spoilage microorganisms

As part of the BierStick project, Fraunhofer IZI worked together with industry and research partners Becit GmbH, Kunststoff-Zentrum in Leipzig gGmbH and Universal Laborservice GmbH to develop a simple system for analyzing beer from a molecular biology perspective without laboratory involvement.

Beer-making is based on fermentation, a process whereby organic substances are transformed during the growth of specific microorganisms. To ensure the quality of the beverage, the microbiology involved in this process has to be strictly controlled. Yeasts take on the leading role here, converting various nutritional components from raw materials into carbon dioxide and alcohol. Various fungi and bacteria are also involved in different stages of production; some of these, however, can have a negative impact on beer quality, making the product no longer fit for consumption. Before market release, beer must therefore be tested for these types of harmful microorganisms.

The test platform developed as part of this project enables a quick and effective molecular detection of harmful and / or spoilage microorganisms. To do this, a sample is taken and concentrated. The nucleic acids from the microbial cells are then released by lysis and the specific genetic sequences are subsequently reproduced by means of RT-LAMP (real-time loop-mediated isothermal amplification). Harmful microorganisms can be identified through the differentiated detection of amplified sequences without having to use additional devices.



1. Microorganisms from the beer sample are concentrated by means of filtration. 2. The microorganisms are lysed on the filter with a lysis buffer. 3. The lysate is applied to the BierStick chip. 4. The nucleic acids taken from living microorganisms are amplified in RT-LAMP. 5. The amplified products are bound specific to their genus on the integrated test strips. 6. The results can be evaluated with the naked eye: here for example, positive for *Lactobacillus* (Lb), *Pediococcus* (Pd) and *Pectinatus* (Pc), negative for *Megasphaera* (Ms); K – control line.

Drawing on its expertise in sample preparation methods, Fraunhofer IZI devised an integrated form of nucleic acid filtration as part of this project. Beyond this, the Fraunhofer team developed an isothermal form of nucleic acid amplification using RT-LAMP in an integrated chip format. The two methods facilitate the selective detection of living beer contaminants.

The project was funded by the German Federal Ministry for Economic Affairs and Energy (now: Federal Ministry for Economic Affairs and Climate Action) as part of the Central Innovation Programme for SMEs.

### Partners

Becit GmbH; Kunststoff-Zentrum in Leipzig gGmbH; Universal Laborservice GmbH

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## Further selected projects

# Integrated molecular diagnostics for the rapid detection of food contaminants



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As part of the CampyTube project, Fraunhofer IZI is developing a simple test system for the rapid diagnosis of microorganisms (*Campylobacter* spp.). *Campylobacter* bacteria count among the most common causes of bacterial gastrointestinal infections in humans. The bacteria are mainly transmitted through contaminated meat. If, for example, the intestines are damaged while being removed from the animals during meat processing, bacteria can find their way onto the skin and meat of the slaughtered animal. This concerns raw poultry in particular. The risk of infection during preparation is then especially high when other foodstuffs are being processed at the same time and come into contact with work surfaces or appliances contaminated by raw poultry meat.

The CampyTube test system is designed to help minimize the risk of transmitting microbial contamination at the stage of meat production and processing. It is being developed for on-site use in poultry keeping, slaughtering and butchering businesses and is expected to enable the detection of

pathogens within a maximum of 45 minutes, without having to first cultivate or accumulate them. This is achieved using an isothermal form of nucleic acid amplification, which is combined with a simple lysis method.

The primary focus of the Fraunhofer IZI research team here is to develop a test that can be performed without any prior knowledge of laboratory technology so that it can be used on site during slaughtering for quality control and contamination prevention. Similar to a pregnancy test, users should be able to read the test result directly from the test. This will enable the staff at the slaughtering house to perform the test without the need for technical support.

The CampyTube test system is initially being developed to detect *Campylobacter* bacteria; it is, however, primarily a technology platform that could, in the future, also be transferred to other bacteria or food contaminants (e.g. salmonella). CampyTube is planned to be used for monitoring surface hygiene in poultry keeping and production, but it can also be used to test meat products. The project is funded by the German Federal Ministry of Food and Agriculture.

### Partners

Hygiene Diagnostics GmbH; Plukon Storkow GmbH

Gefördert durch



aufgrund eines Beschlusses  
des Deutschen Bundestages



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## Further selected projects

# Glyco3Display: DNA-based arrangement of glycans for new analysis methods

Polysaccharides, also known as glycans, are long and complex sugar molecules made up of a chain of monosaccharides such as mannose, glucose or fructose. Pathogenic bacteria or viruses use these molecules to identify, bind and infect host cells. Sugar molecules found on the membrane of human cells (e.g. mannose, heparin or sialic acid) are therefore particularly interesting from a medical perspective. Furthermore, the geometry of the polysaccharides in the nanometer range plays a decisive role as pathogens use two or three sugar-binding receptors to increase their binding affinity and more efficiently infect the target.

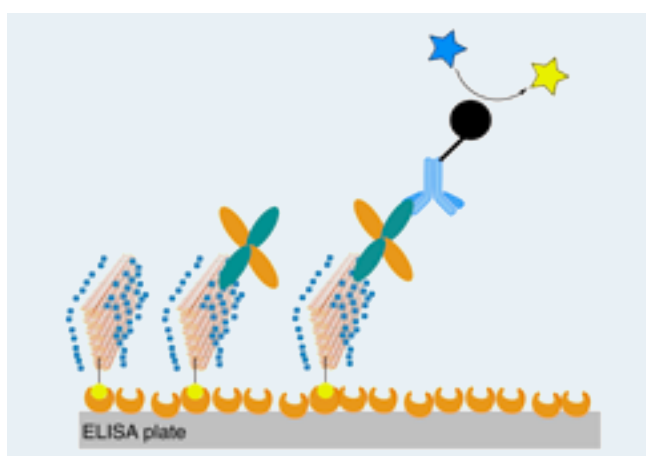
In the Glyco3Display project, novel compounds were created by combining various glycan molecules and DNA-based structural scaffolds. This approach enabled precise arrangements of defined glycan chains to be manufactured with a spatial resolution of one nanometer. The project merged two key technologies from partners Fraunhofer IZI and Max Planck Institute of Colloids and Interfaces: DNA nanotechnology and automated glycan synthesis.

The focus was placed on developing high-throughput assays to examine the bond of specific glycan compositions and arrangements on target pathogens or glycan-binding proteins. To this end, glycosylated DNA nanostructures were integrated into two analytical standard platforms which are accessible to researchers all around the world.

First, by affixing the DNA glycan compounds to microbeads using flow cytometry, it was able to be quantified how the glycan composition and its geometric arrangement on the DNA scaffolds affect its ability to bind to the surface of disease agents such as *E. coli* or *K. pneumoniae*. Alternatively, different types of DNA glycan nanostructures were integrated into classic ELISA tests. This meant that different combinations of sugars, geometries and conjugation strategies were able to be tested in order to produce the strongest interactions with glycan-binding proteins, known as lectins. Compared to existing methods, the project team was able to quickly test out many ligand candidates using these two procedures and control the geometric arrangement in which they were presented to the target proteins.

### Partners

Max-Planck-Institute of Colloids and Interfaces



*Almost 100 sugar molecules were conjugated on large "DNA origami" nanostructures consisting of several hundred DNA oligonucleotides. Should these be integrated into ELISAs, they could replace the standard antibodies that are used to capture or recognize targets in immunodiagnostics.*

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## Further selected projects

# Establishing and testing effective ways of investigating structure-activity relationships by means of protein crystallography



Researchers at Fraunhofer IZI are working on establishing effective techniques that can be applied to investigate structure-activity relationships using protein crystallography. Across four subprojects, they are defining and characterizing the respective structure and interactions of proteins (targets) with drug molecules using X-ray crystallography.

In the first subproject, the project team is analyzing the binding modes of novel, proprietary active agents by dismantling each of the complex structures of human glutaminyl cyclase and meprin beta using respective drug molecules. This is a precondition to being able to develop patentable prototypes that could be used in an early therapy for Alzheimer's disease.

The second subproject focuses on the shape and form of the binding pocket of a monoclonal antibody, which is also of interest for the treatment of Alzheimer's. The specific binding properties are to be derived here from the collected data, which will then provide a basis for further biochemical evaluation.

In the third subproject, the team of researchers is analyzing the proteins thaumatin II and brazzein, which are to be used as sweeteners and sugar substitutes in the food industry. In doing this, protein variants from more productive host plants will be analyzed and compared with the original protein variant.

The fourth research project focuses on lectins. Several lectin-based, nasally administered product candidates designed to protect against infection with corona and influenza viruses are currently undergoing clinical testing. In order to make statements relating to form and details on a molecular level and thus about interactions, a structure determination and binding characterization will first be carried out.

The project "Establishing and testing effective ways of investigating structure-activity relationships by means of protein crystallography (EtaPPro)" is supported by the Land of Saxony-Anhalt using funds provided by the European Regional Development Fund (ERDF). The investigations are important not only for establishing new molecular strategies for the treatment of diseases, but also for the further development of other protein-based approaches.



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## Further selected projects

# Improving the diagnosis and treatment of prostate cancer using big data analyses

Since 2018, Fraunhofer IZI has been an active member of the EU's PIONEER consortium (Prostate Cancer DiagnOsis and TreatmeNt Enhancement through the Power of Big Data in EuRope), a cluster of excellence for big data analyses relating to prostate cancer. The consortium comprises 32 partners from nine European countries. The collaboration aims to improve the care of prostate cancer patients by generating and analyzing large volumes of scientific and clinical data. A key role is assigned here to the standardization and integration of existing data from a broad range of sources, which is to be pooled in an innovative open-access platform for research purposes. Fraunhofer IZI is contributing to the consortium primarily by offering its expertise in the data harmonization of transcriptome-wide expression studies and statistical analyses for biomarker identification and confirmation.

The PIONEER working group for molecular data led by Fraunhofer IZI carries out research first and foremost into the deregulation of signaling pathways at molecular level seen in prostate cancer. For specific signaling pathways, the scientists will characterize the type of molecular changes, their prevalence and the prognostic impact. The spotlight is being shone here on the transcriptome level. To help with this work, the team is able to draw on extensive preliminary studies and data sets: transcriptome data sets containing clinical data and follow-ups for more than 1800 patients are available, for example, as is single-cell RNA sequencing data from around 90,000 cells from five studies. Both the correlation between expression and prognosis as well as the expression in different

cell types (PCa single cell atlas) are to be depicted using the data. The results will round out the PIONEER platform.

The PIONEER consortium is funded by the IMI2 joint undertaking, listed under grant agreement number 777492. It forms part of the Big Data for Better Outcomes (BD4BO) program. IMI2 receives support through the EU's Horizon 2020 Research and Innovation Programme and the Federation of Pharmaceutical Industries and Associations (EFPIA).

The above text represents solely the perspective of Fraunhofer IZI.

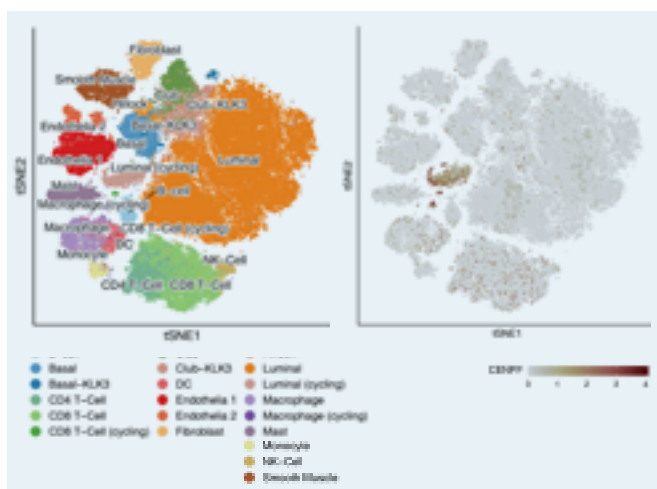
<https://prostate-pioneer.eu>

### Partners

PIONEER consortium, coordinator: European Association of Urology

### Contact

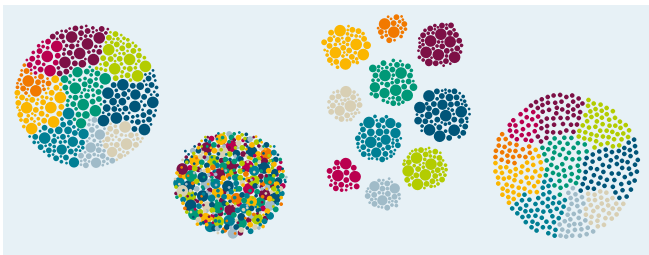
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PCa single cell atlas: Integrated illustration of 90,000 cells and annotation of the cell type (left). Depiction of the expression of individual genes, e.g. prognostic markers (right).

## Further selected projects

# Foundations for new, Europe-wide standards in drug development



*Illustration of the various levels of molecular characterization of tissue samples (f.l.t.r.): composition of the original tissue (different cell populations are shown in different colors), sequencing of a cell mixture (bulk transcriptomics), sequencing of individual cells (single-cell sequencing) and spatially resolved sequencing (spatial transcriptomics).*

The EU consortium imSAVAR (Immune Safety Avatar: non-clinical mimicking of the immune system effects of immunomodulatory therapies) aims to lay the groundwork for new, Europe-wide standards in drug development. A significant challenge facing the development of new therapies is their preclinical evaluation in terms of efficacy and safety. This is, first and foremost, due to the complexity of the human immune system. When a person is ill, for example in the case of cancer, autoimmune or inflammatory diseases, the cells of the immune system interact differently to those of a healthy person. As preclinical tests have so far mainly looked at the underlying toxicity of new therapeutic agents in terms of the (healthy) immune system, there is a lack of non-clinical models that precisely capture the individual interactions of the human immune system in the pathogenic state.

The EU consortium imSAVAR addresses this deficiency by offering new concepts for testing immunomodulatory therapies. The goal here is to improve existing and develop new model systems in order to identify any undesirable side effects of new therapies on the immune system. Moreover, new biomarkers for the diagnosis and prognosis of immune-mediated pharmacologies and toxicities are also to be developed.

The interdisciplinary imSAVAR consortium comprises 28 international partners from eleven nations, including university and non-university research facilities, pharmaceutical and biotechnology companies, and regulatory authorities. Besides overseeing the scientific coordination of the overall project, Fraunhofer IZI focuses in particular on predicting and evaluating adverse effects caused by novel immunotherapies developed for oncological and inflammatory diseases. This involves optimizing and developing respective models (in situ, in vitro, in vivo, in silico), taking into account biomarkers that depict the complexity of the modes of action typical of immunotherapies. To do this, Fraunhofer IZI and partners from the consortium are looking to the characterization of patients who receive CAR-T cell therapy. Patients showing signs of adverse effects will undergo extensive molecular and cellular companion diagnostics as part of a multicenter research study. The objective here is to identify characteristics which will be integrated into non-clinical models in the future in order to significantly improve the prediction of toxicities caused by new CAR-T cell therapies.

### Project coordination

Fraunhofer IZI / Novartis AG

<https://imsavar.eu>



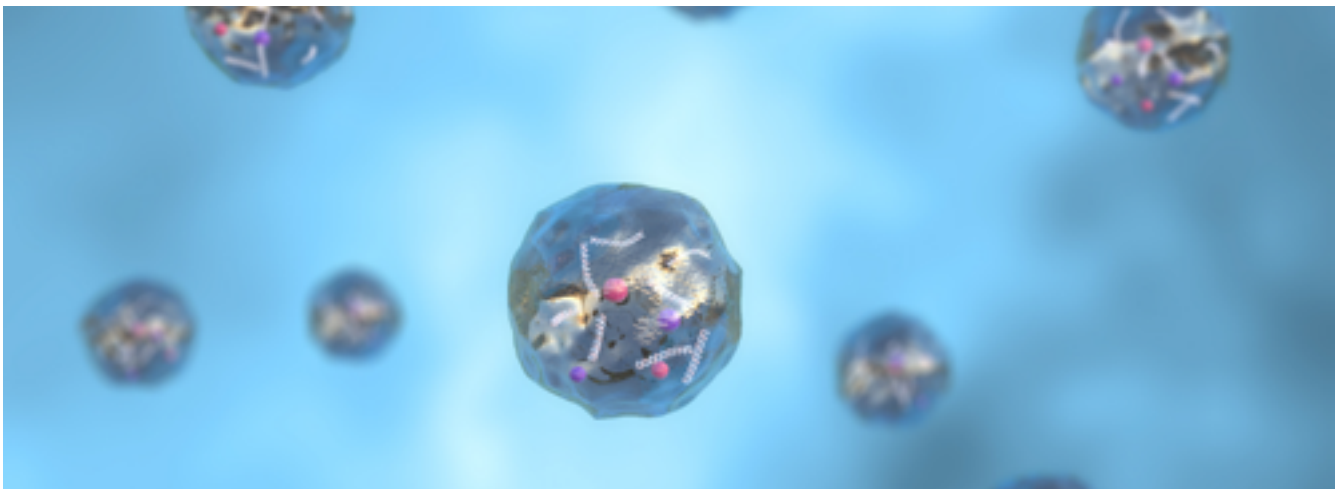
*The project is financed by the joint undertaking "Innovative Medicines Initiative" (IMI2 joint undertaking). IMI2 is supported by the EU Horizon 2020 program and the European Federation of Pharmaceutical Industries and Associations (EFPIA).*

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## Further selected projects

# Extracellular vesicles for modulation of the immune system



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With an incidence of 30–60 percent, graft-versus-host disease (GvHD) is one of the main complications to follow allogeneic hematopoietic cell transplantation. Conventional treatment methods target a nonspecific suppression of the immune system, which can significantly increase the risk of infection and relapse. It is therefore all the more important that new drugs and therapeutic approaches are developed which, in the best case, maintain the function of a patient's immune system while reducing adverse effects.

For several years now, extracellular vesicles (EVs) have been at the center of various research approaches relating to immune-mediated inflammatory diseases. Alongside a

variety of diagnostic applications, anti-inflammatory and immunomodulatory effects are of particular interest to researchers. Almost every cell secretes EVs and a high number of cells resorb them. They thus play a fundamental role in intercellular communication and assume an important role in preserving physiological balance and in the pathogenesis of different diseases.

Measuring some 50 to 2000nm in size, the vesicles transport an abundance of biomolecules (including proteins, nucleic acids, lipids and metabolites). Immunomodulatory effects were able to be observed in various in vitro and in vivo studies, for example through EVs from stem cells.

On behalf of the company Lysatpharma GmbH (Eisenberg), whose technological focus lies in the field of regenerative medicine and the development of novel immunotherapies based on EVs, Fraunhofer IZI is evaluating the preventive and therapeutic potential of EVs in an in vivo GvHD model (mouse). Lysatpharma GmbH received support to carry out this preclinical research and product development through an economic development grant awarded to individual businesses by the Free State of Thuringia (project number 2019 FE 0152 (EFRE)).

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## Overview

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# EU and joint projects

### Mature NK (EU / Horizon 2020)

- Manufacturing Tumor Reactive Natural Killer Cells
- Coordination: Fraunhofer IZI

[www.mature-nk.eu](http://www.mature-nk.eu)

### AIDPATH (EU / Horizon Europe)

- AI powered, Decentralized Production for Advanced Therapies in the Hospital
- Coordination: Fraunhofer

[www.sciencrow.com/c/6499?title=AIDPATH](http://www.sciencrow.com/c/6499?title=AIDPATH)

### REANIMA (EU / Horizon Europe)

- Prevent heart failure by reawakening the endogenous regenerative ability of the mammalian heart
- Coordination: Spanish National Center for Cardiovascular Research

[www.reanima2020.eu](http://www.reanima2020.eu)

### REMEDI4ALL (EU / Horizon Europe)

- European Platform for Medicines Repurposing
- Coordination: EATRIS ERIC

[www.remedi4all.org](http://www.remedi4all.org)

### ImSavar (EU / IMI)

- Nonclinical mimicking of the immune system effects of immunomodulatory therapies
- Coordination: Fraunhofer IZI / Novartis AG

[www.imsavar.eu](http://www.imsavar.eu)

### T2Evolve (EU / IMI)

- Accelerating Development and increasing awareness and access of patients with cancer to immunotherapy
- Coordination: University Hospital Würzburg

[www.t2evolve.com](http://www.t2evolve.com)

### RNAuto (Fraunhofer)

- Automated production of mRNA-based vaccines and gene therapeutics
- Coordination: Fraunhofer IZI

<https://s.fhg.de/rnauto>

### SaxoCell (BMBF / Clusters for Future)

- Precision medicine by cell and gene therapies
- Coordination: Fraunhofer IZI / TU Dresden

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

### WIR! sind DIANA (BMBF)

- Technologies for future point of care diagnostics
- Coordination: Fraunhofer IZI / Fraunhofer IWU

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



# 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.

## Sponsors

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.



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## Advisory Board

The advisory board functions as the external expert committee for strategic questions regarding the institutional direction and the Fraunhofer-Gesellschaft. Its members are invited and appointed by the president of the Fraunhofer-Gesellschaft. The advisory board includes representatives from industry and research as well as from authorities, ministries and foundations. The board meets once a year and evaluates the performance and image of the institute.

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# The Fraunhofer-Gesellschaft

The Fraunhofer-Gesellschaft based in Germany is the world's leading applied research organization. Prioritizing key future-relevant technologies and commercializing its findings in business and industry, it plays a major role in the innovation process. It is a trailblazer and trendsetter in innovative developments and research excellence. The Fraunhofer-Gesellschaft supports research and industry with inspiring ideas and sustainable scientific and technological solutions and is helping shape our society and our future.

The Fraunhofer-Gesellschaft's interdisciplinary research teams turn original ideas into innovations together with contracting industry and public sector partners, coordinate and complete essential key research policy projects and strengthen the German and European economy with ethical value creation. International collaborative partnerships with outstanding research partners and businesses all over the world provide for direct dialogue with the most prominent scientific communities and most dominant economic regions.

Founded in 1949, the Fraunhofer-Gesellschaft currently operates 76 institutes and research units throughout Germany. Over 30,000 employees, predominantly scientists and engineers, work with an annual research budget of €2.9 billion. Fraunhofer generates €2.5 billion of this from contract research. Industry contracts and publicly funded research projects account for around two thirds of that. The federal and state governments contribute around another third as base funding, enabling institutes to develop solutions now to problems that will become crucial to industry and society in the near future.

The impact of applied research goes far beyond its direct benefits to clients: Fraunhofer institutes enhance businesses' performance, improve social acceptance of advanced technology and educate and train the urgently needed next generation of research scientists and engineers.

Highly motivated employees up on cutting-edge research constitute the most important success factor for us as a research organization. Fraunhofer consequently provides

opportunities for independent, creative and goal-driven work and thus for professional and personal development, qualifying individuals for challenging positions at our institutes, at higher education institutions, in industry and in society. Practical training and early contacts with clients open outstanding opportunities for students to find jobs and experience growth in business and industry.

The prestigious nonprofit Fraunhofer-Gesellschaft's namesake is Munich scholar Joseph von Fraunhofer (1787–1826). He enjoyed equal success as a researcher, inventor and entrepreneur.

Figures as of: January 2022

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Prof. Dr. Axel Müller-Groeling | Member of the Executive Board  
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and for additional contact information

**([www.izi.fraunhofer.de/en/contact.html](http://www.izi.fraunhofer.de/en/contact.html))**





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