Fraunhofer IZI

Fraunhofer Institute for Cell Therapy and Immunology IZI

Fraunhofer IZI

Annual report 2021 / 2022

Table of contents

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.

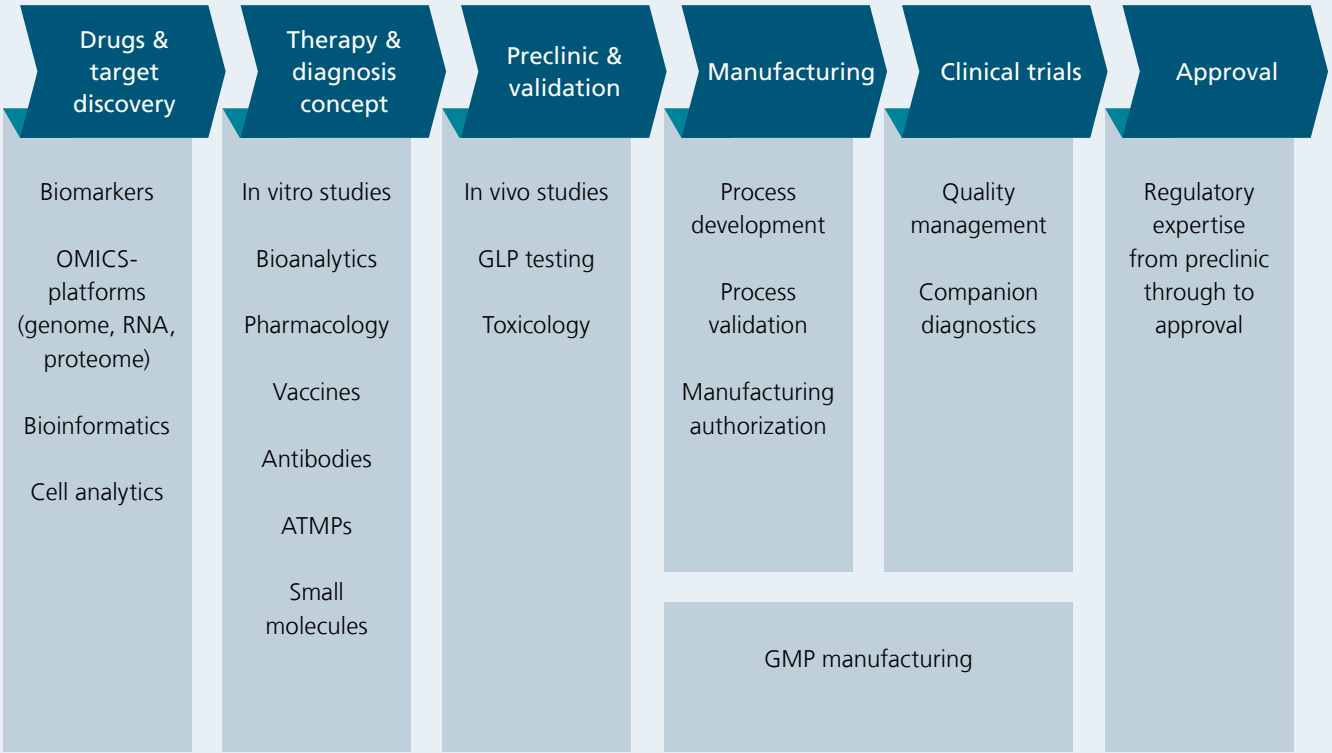
Business units and competencies

Cell and gene therapy

Drugs and vaccines

Molecular and immunodiagnostics

Extracorporeal therapies



Organization

Director
Prof. Dr. Dr. Ulrike Köhl (executive)
PD Dr. Sebastian Ulbert (deputy)

Administration
Anja Bochmann-Seidel
Annette Schäfer (deputy)

Executive departments

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

Central facilities

Officers

Department of GMP Cell and Gene Therapy

Dr. Gerno Schmiedeknecht
Kati Kebbel

Department of GMP Process Development / ATMP Design

PD Dr. Stephan Fricke

NK Cell Engineering
Dr. Dominik Schmiedel

Department of Preclinical Development and Validation

Dr. Jörg Lehmann

Toxicology and Immuno-toxicology
Sina Riemschneider
Inflammation and Tumor Models
Claudia Müller
Proteomics
Prof. Dr. Stefan Kalkhof

Department of Vaccines and Infection models

PD Dr. Sebastian Ulbert
PD Dr. Thomas Grunwald

Vaccine Technologies
Dr. Jasmin Fertey
Preclinical Validation
PD Dr. Thomas Grunwald
Vector-based Immunotherapy
Prof. Dr. Hildegard Büning
Prof. Dr. Ulrich Hacker
Antimicrobial Biotechnology
Dr. Belinda Loh

Department of Diagnostics

Dr. Dirk Kuhlmeier

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

Department of Extracorporeal Therapy Systems

Rostock

Prof. Dr. Steffen Mitzner

Department of Drug Design and Target Validation

Halle (Saale)

Prof. Dr. Stephan Schilling

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

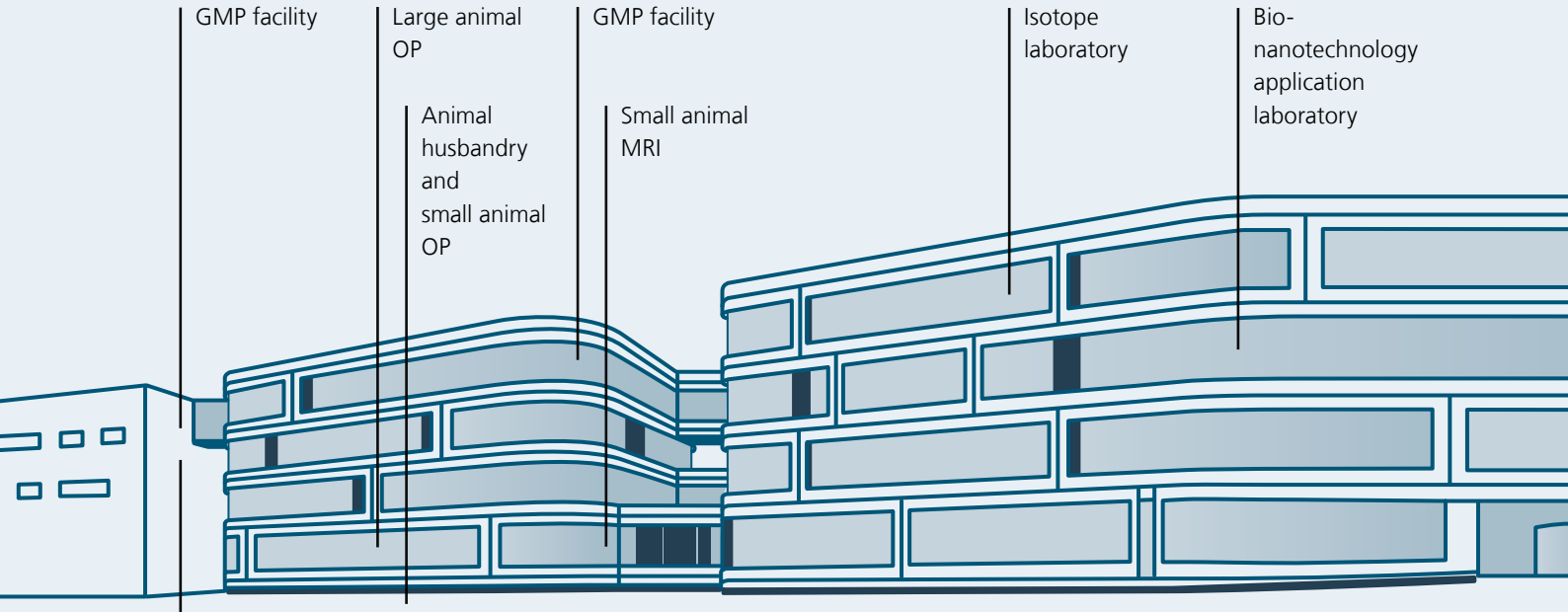
Branch Bioanalytics and Bioprocesses

Potsdam-Golm

Dr. Eva Ehrentreich-Förster (deputy)

April 1, 2022

Research infrastructure at the Leipzig site



First extension building

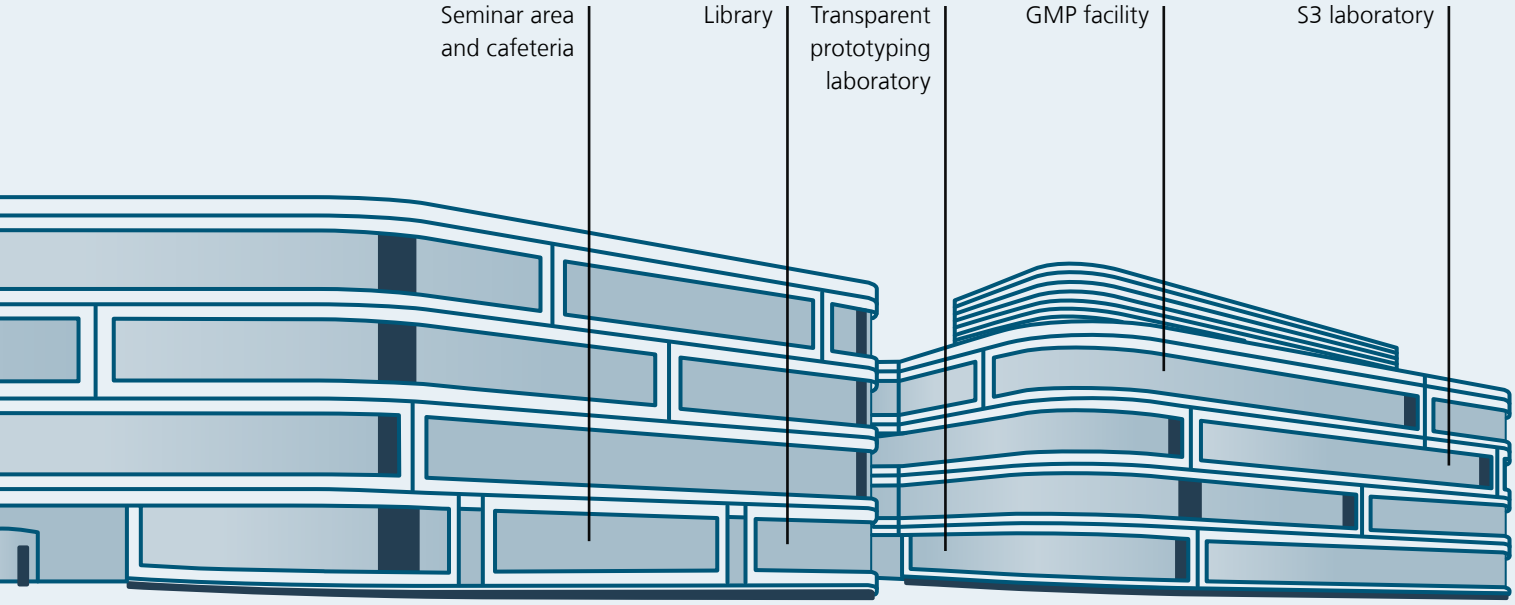
Usable area: 1 568 m²
Lab space: 470 m²
Offices: 142 m²
Clean rooms: 410 m²

Main building

Usable area: 4 131 m²
Lab space: 1 867 m²
Offices: 1 615 m²
Seminar area: 276 m²

Rental area at BIO CITY Leipzig

Clean rooms: 334 m²

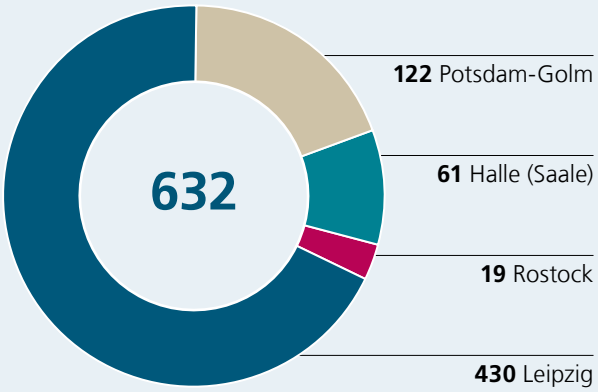


Second extension building

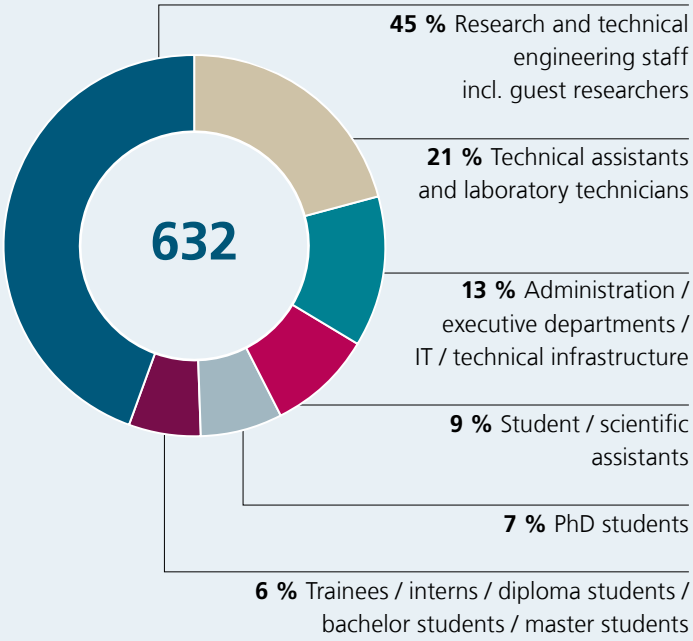
Usable area: 3 050 m²
Lab space: 1 171 m²
Offices: 881 m²
Clean rooms: 402 m²

Key institute figures 2021

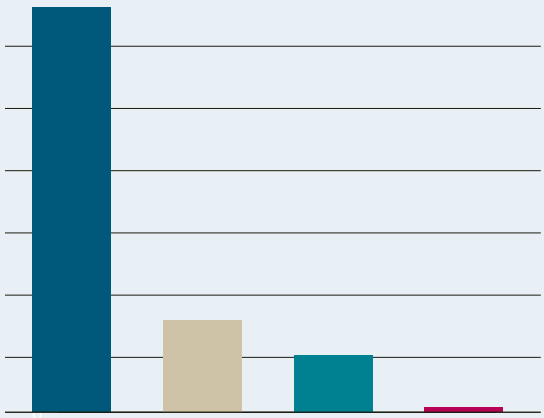
Employees
by location



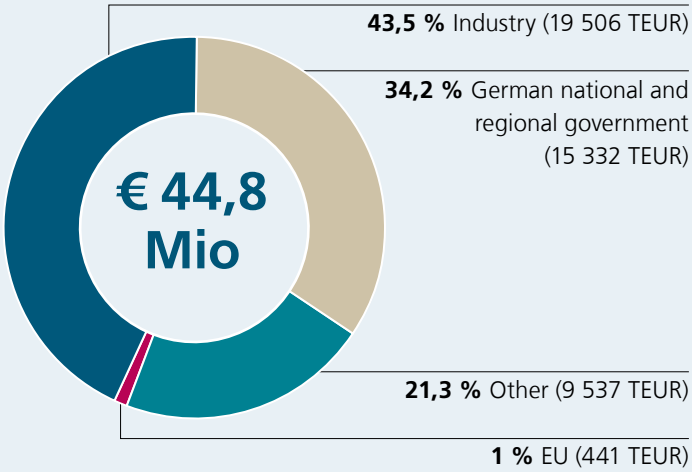
Employees
workforce composition



€ 44,8 Mio project revenue
by location in € mio



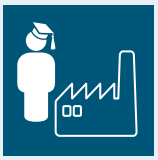
Project revenue
by funding agency



December 31, 2021

Scientific presence and network 2021

110 Conventions and conferences



102 Industry partners
126 Research partners

74 Abstracts
83 Publications
2 Book articles

56 Teaching activities

6 Doctorates
1 Diploma theses
21 Master theses
12 Bachelor theses

56 Patent families
304 Patents and patent applications

50 Evaluator activities

100 Association memberships in various expert associations

Detailed information on the key figures and publications can be found on our website at
www.izi.fraunhofer.de/en/publications

Locations and departments

Headquarter

Leipzig, Saxony, Germany

The main building boasts extensive laboratory capacities for conducting molecular and cell-biological work. An extensive immuno-histochemistry 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 head-quarters 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 m².

www.izi.fraunhofer.de/en

Management

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Department of GMP Cell and Gene Therapy

Leipzig, Saxony, Germany

The Department of GMP Cell and Gene Therapy operates Fraunhofer IZI's three modern GMP facilities consisting of ten separate clean room suites (altogether 21 clean room grade B manufacturing rooms) which have been specially optimized for manufacturing of cell and gene therapy products, so called Advanced Therapy Medicinal Products – ATMP. The particular specialty of the about 100 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

- Quality assurance
- 1 000 m² clean rooms
- ATMPs
- GMP process and method transfer
- Manufacturing authorization according to §13 AMG
- Investigator Medicinal Product Dossier (IMPD)
- Good Manufacturing Practice (GMP)
- Manufacturing and quality control of ATMPs

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Department of GMP Process Development / ATMP Design

Leipzig, Saxony, Germany

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

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

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

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

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

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

Core competencies

- GMP process development and transfer for ATMP manufacturing
- mRNA technology
- Specialist expertise in hematology / oncology
- Process optimization and automation
- Good Manufacturing Practice (GMP) evaluation for ATMP manufacturing
- Quality assurance
- GMP-compliant equipment and processes
- Clinical trial planning
- CAR-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)

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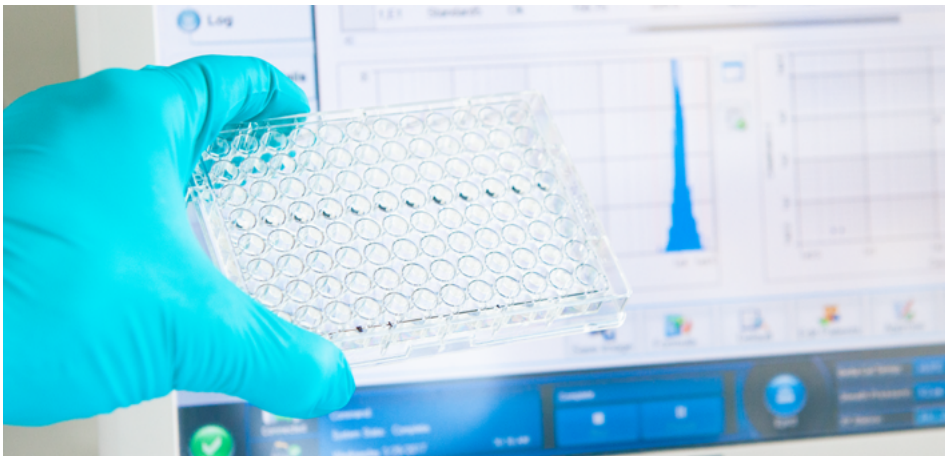
Department of Preclinical Development and Validation

Leipzig, Saxony, Germany

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
- Immunotoxicology (study design and implementation)
- Protein biomarker (identification and validation)
- Antibody and immunoassay development (diagnostics)
- Antibody development (therapy)

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Department of Vaccines and Infection Models

Leipzig, Saxony, Germany

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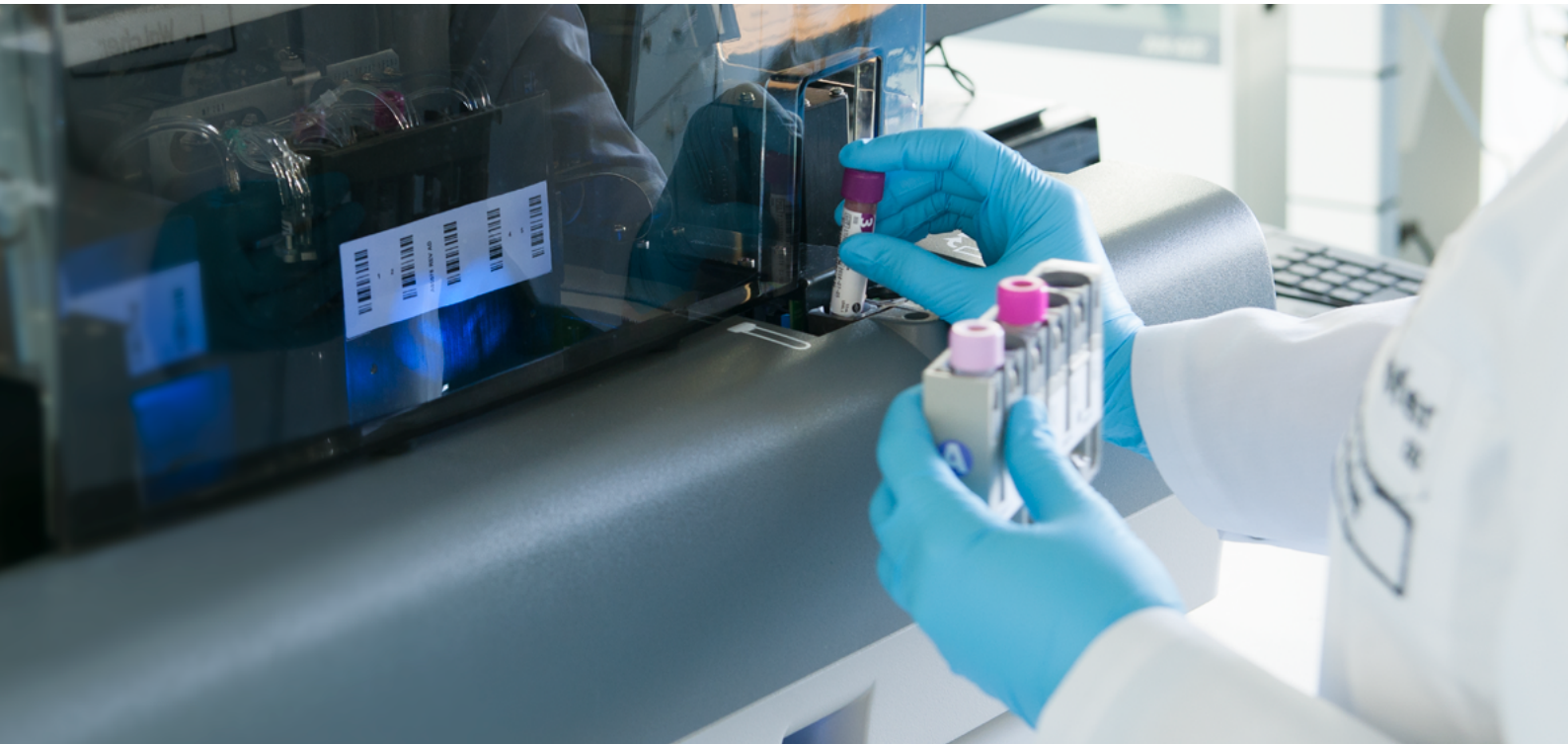
Procedures to stimulate or suppress the immune system are developed in the Department of Vaccines and Infection Models. These include vaccines on innovative technology platforms, e.g. novel inactivation methods or plasmid DNA. As such, efficient vaccines can be produced quickly and inexpensively. An 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



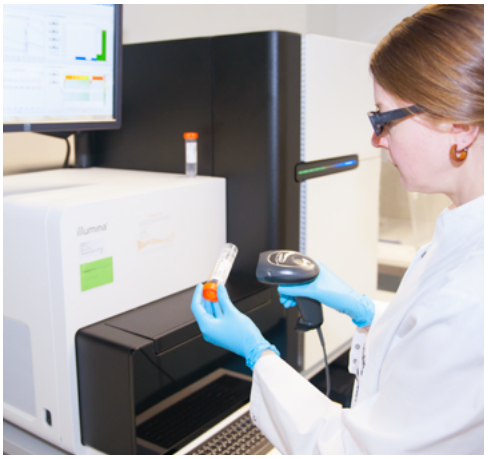
Department of Diagnostics

Leipzig, Saxony, Germany

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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Department of Extracorporeal Therapy Systems

Rostock, Mecklenburg-Western Pomerania, Germany

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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

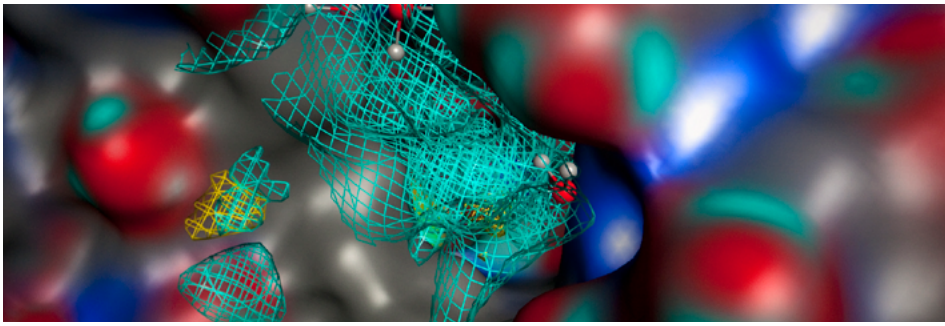
- Cellular biosensors
- Medical devices for blood purification
- Dialysis procedure
- Organ-supporting technologies

Department of Drug Design and Target Validation

Halle (Saale), Saxony-Anhalt, Germany

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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Branch Bioanalytics and Bioprocesses

Potsdam-Golm, Brandenburg, Germany

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

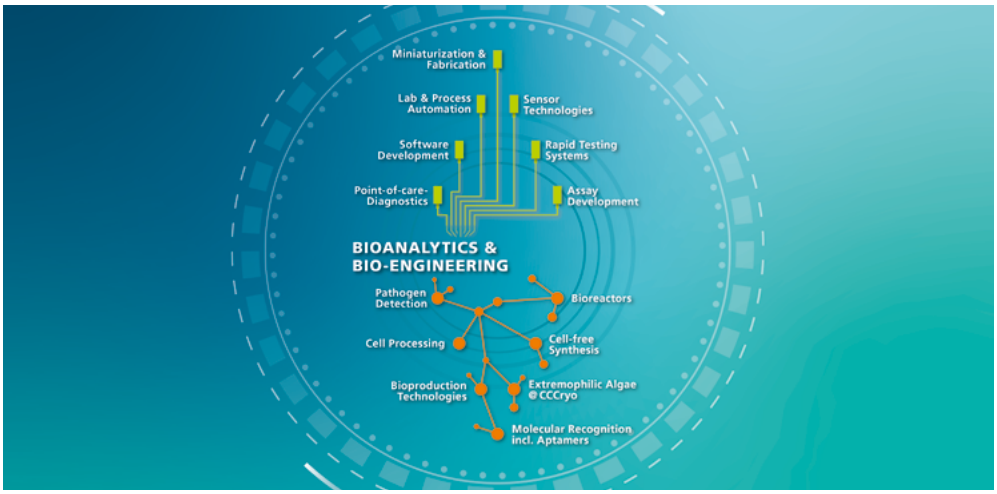
The interdisciplinary team comprising natural scientists, engineers and technicians develops powerful, analytical methods for the detection and validation of pathogens and biological markers besides processes to obtain, handle and manipulate cells and biomolecules. In this context, the team develops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

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

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

www.izi-bb.fraunhofer.de/en.html

www.izi-bb.fraunhofer.de/en/media/annual-report.html



Management

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Project Center Microelectronic and Optical Systems for Biomedicine

Erfurt, Thuringia, Germany

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

Involved Fraunhofer institutes

Fraunhofer Institute for Applied Optics and Precision Engineering IOF
www.iof.fraunhofer.de/en

Fraunhofer Institute for Photonic Microsystems IPMS
www.ipms.fraunhofer.de/en

Fraunhofer Institute for Cell Therapy and Immunology IZI
www.izi.fraunhofer.de/en

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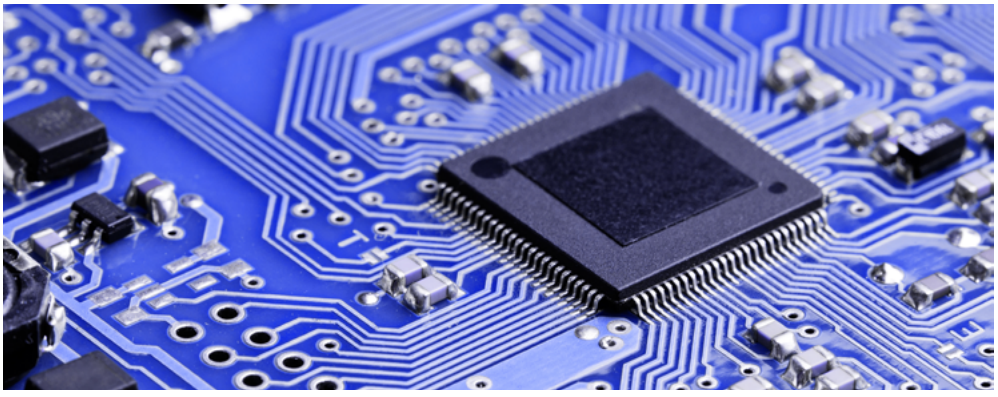

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Central facilities

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

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

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 three 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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Imaging and image analysis

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

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

In vivo Imaging

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

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

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

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

Fluorescence and bioluminescence imaging for small animals

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

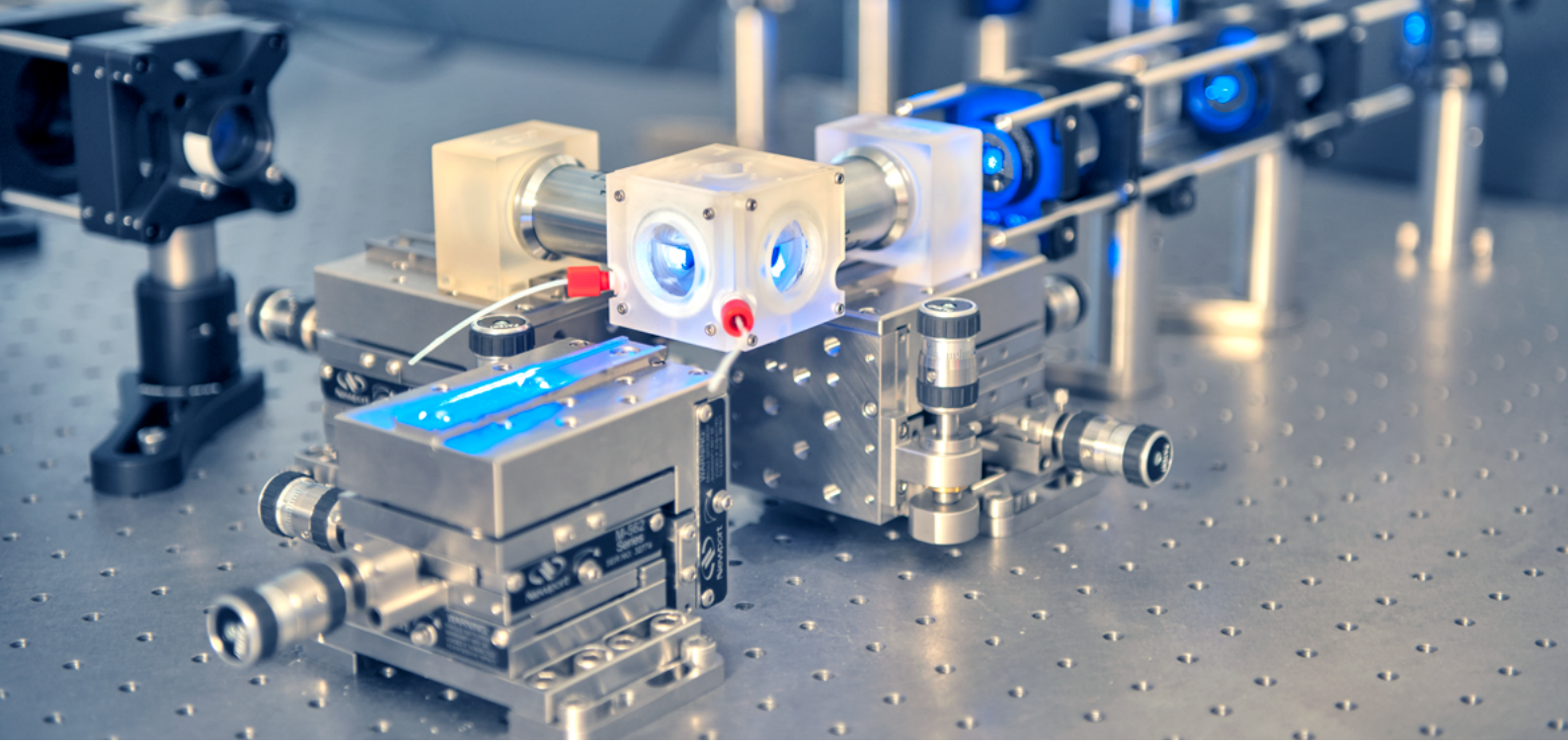
Bedside imaging for small animals

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

In vitro / Ex vivo imaging

Clearing tissue samples

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



Confocal laser scanning microscope with live cell imaging

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

Light sheet microscopy

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

Atomic force microscopy

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

MALDI Mass Spectrometry Imaging (MALDI-MSI)

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

Laser capture microdissection

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

Hardware-linked evaluation process

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

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Center for Experimental Medicine

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

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

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

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

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

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

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

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

Equipment and services:

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

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

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

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

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

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RIBOLUTION Biomarker Center


Zertifikat

Prüfungsnorm: ISO 9001:2015

Zertifikat-Registrier-Nr.: 01 100 2000010

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

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

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

Gültigkeit: Dieses Zertifikat ist gültig vom 23.07.2020 bis 22.07.2023.

10.08.2020

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

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

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

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 m³/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 (TCID50, plaque assay), and virus inactivation. Neutralization assays can also be carried out.

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

Achievements and contract research

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

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Fraunhofer Prize for “Human- and Environment-Centered Technology”

Fraunhofer Prize for "Human- and Environment-Centered Technology" 2021

For a vaccine production process that is faster, more efficient and more environmentally friendly

This process for the production of inactivated vaccines, which was jointly developed by Fraunhofer IZI, the Fraunhofer Institute for Organic Electronics, Electron Beam and Plasma Technology FEP from Dresden and Fraunhofer Institute for Manufacturing Engineering and Automation IPA, received the Fraunhofer Prize for "Human- and Environment-Centered Technology". The prize, which is endowed with EUR 50,000, was presented at the Annual Fraunhofer Society Conference on 5 May 2021.

This method using low-energy electron beams is more efficient, faster and more environmentally friendly than the conventional production method. The jury praised "the simple and efficient method largely retaining the structures important for the efficacy of the vaccine while completely avoiding chemical additives which would otherwise be required".

We would like to thank all colleagues for their contribution to the development of this innovative method together with PD Dr Sebastian Ulbert and Dr Jasmin Fertey of Fraunhofer IZI, Frank-Holm Rögner of Fraunhofer FEP and Martin Thoma of Fraunhofer IPA.

A detailed description of the project is provided on page 58 and at **https://s.fhg.de/fraunhofer-prize.**

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Selected projects

EU and joint projects

Spokesperson

Prof. Dr. Dr. Ulrike Köhl
Fraunhofer IZI & University of Leipzig Medical Center

Prof. Dr. Ezio Bonifacio
Technische Universität Dresden

CLUSTERS 4 FUTURE
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GEFÖRDERT VOM
Bundesministerium für Bildung und Forschung

SaxoCell

Fraunhofer IZI is part of the SaxoCell consortium.

The concept for a Saxon future cluster on "living medical products" was selected for implementation together with six other projects from a total of 137 applicants in the "Clusters4Future" innovation competition of the Federal Ministry of Education and Research (BMBF). Over the coming years, this consortium will develop new fields of application and production methods for gene and cell therapeutics. The aim is to produce cells with precisely defined functions and a high safety profile for safe clinical use on an industrial scale and at socially acceptable costs in order to enable a realistic and sustainable economic model with high value-added potential for the region.

Fraunhofer IZI contributes its competences in the field of cell technologies, in particular, the development and production of genetically modified immune cells (e.g. CAR NK cells and CAR T cells). Both AAV-based gene transfer technologies and non-viral methods, such as the Sleeping Beauty transposon technology, are used in this. In addition, pharmaceutical productions processes are being developed and established, e.g. for an antibody-modified stem cell transplant (Palintra®). These will then be evaluated in clinical studies (phases I/II). Fraunhofer IZI contributes its experience in the collection and biostatistical analysis of cell and molecular biological datasets to the SaxoCellOmics technology platform.

www.saxocell.de/en

Fraunhofer lead project RNAuto: Automated production of mRNA vaccines

In future, innovative drugs, such as novel vaccines as well as gene and cell therapeutics based on mRNA, are to be made available to a large patient population within an affordable healthcare system. This will need automated production technologies that safely and reliably manufacture these products in accordance with the high requirements put to medical products (GMP certification). Therefore, this consortium brings together interdisciplinary competences from medicine, biology and engineering to develop an AI-controlled, digitized and automated production process within the meaning of industries 4.0.

The project partners are using two drug candidates to demonstrate process automation: One of these is an mRNA vaccine providing protection against the West Nile fever, a viral disease, while the other candidate concerns mRNA-induced gene therapeutics against cancer which are based on healthy donors' natural killer cells.

The consortium is developing an automated screening system facilitating the speedy process development of mRNA nano-transporters with a digital image for process and quality control as well as an expansion module with integrated quality control for the production of allogenic gene and cell therapeutics. The generally limited stability of mRNA molecules and correct encapsulation of the mRNA in lipid nano-transporters constitute key biological challenges in this process. The research activities focus, in particular, on automation capacity up to industrial scale as well as the scale-up of mRNA, mRNA nano-transporter and mRNA-modified cell production.

Participating Fraunhofer institutes:
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, Fraunhofer Institute for Cell Therapy and Immunology IZI

Project management

Prof. Dr. Dr. Ulrike Köhl
Fraunhofer IZI

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MATURE NK – MAnufacturing TUmor-REactive Natural Killer cells

The MATURE-NK project provides future-oriented training in translational research in order to close the gap between basic research and the applied development of new cell-based therapeutic products by the biotech industry and their clinical application in incurable diseases. This is done using the example of activated genetically modified natural killer cells (NK cells), which are classified as advanced therapy medicinal products (ATMPs). Overall, fourteen partners from nine countries participate in the project which is sponsored by the EU under its Horizon 2020 programme.

Project coordination: Fraunhofer IZI
Grant Agreement No: 765104

www.mature-nk.eu

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REANIMA – New-generation cardiac therapeutic strategies directed to the activation of endogenous regenerative mechanisms

REANIMA aims to provide innovative therapies for heart regeneration. It is the first project in Europe to include results from fundamental research with the aim of translating these into medical applications. The knowledge gained from animal models is to be comprehensively analysed to develop new, regenerative therapies to treat congestive heart failure. This project is funded by the EU Horizon 2020 programme. Fraunhofer IZI is a member of the project consortium which brings together twelve European partners.

Project coordination: Centro Nacional de Investigaciones Cardiovasculares (CNIC)
Grant Agreement No: 874764

www.reanima2020.eu

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AIDPATH – Artificial Intelligence-driven, Decentralized Production for Advanced Therapies in the Hospital

In the EU AIDPATH project, partners from industries and research work on the development of an automated and intelligent system which permits the targeted and patient-specific cell therapy directly at the treatment location, i.e. the hospital. Moreover, this project also focuses on the integration of the system into the hospital environment taking into account logistics processes as well as data management and data security. Fraunhofer IZI supports this project by contributing its expertise, in particular, in the automation of production processes and systems networking. AIDPATH is funded under the EU Horizon 2020 programme.

Project coordination: Fraunhofer-Institut für Produktionstechnologie IPT
Grant Agreement No: 101016909

www.aidpath-project.eu

imSAVAR – Immune Safety Avatar: Nonclinical mimicking of the immune system effects of immunomodulatory therapies

The imSAVAR consortium is intended to lay the foundation for new, Europe-wide standards in drug development. The twenty-eight international partners from eleven countries aim to improve existing model systems and develop new ones in order to identify undesired side effects new treatments have on the immune system. To this end, new biomarkers for the diagnosis and prognosis of immune-mediated pharmacologies and toxicities are to be developed. Moreover, toxicity mechanisms and the potential for reducing such using therapeutic measures are being investigated. imSAVAR is funded by the "Innovative Medicines Initiative" joint undertaking (IMI2 joint undertaking). IMI2 is funded under the EU Horizon 2020 programme and supported by the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Project coordination: Fraunhofer IZI / Novartis AG
Grant Agreement No: 853988

www.imsavar.eu

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T2EVOLVE – Accelerating Development and Improving Access to CAR and TCR-engineered T cell therapy

T2EVOLVE aims to accelerate the development of the CAR T cell therapy within the EU, to expand patients' access to it and, concurrently, to provide guidelines for the sustainable introduction of this cancer treatment within the EU healthcare system. Moreover, the project is designed to contribute to a reduction of the financial burden which healthcare puts on the economy and on society. By including patients this project ensures that the focus is on the cancer patients' perspective – both in research and in cancer treatment. The twenty-seven partners from nine European countries include university and non-university research facilities, such as Fraunhofer IZI, pharmaceutical and bio-technology companies, SMC as well as regulatory authorities, patients' and professional associations. T2EVOLVE is funded by the Innovative Medicines Initiative 2 Joint Undertaking. This joint undertaking is supported by the EU Horizon 2020 programme and by the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Project coordination: University Hospital Würzburg
Grant Agreement No: 945393

www.t2evolve.eu

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Corona pandemic

United against corona – Fraunhofer experts are on the front line in the fight against Covid-19, helping the economy and society to overcome the immediate effects and future consequences of the pandemic. Fraunhofer IZI is involved in various projects aimed at investigating, developing and optimizing solutions for diagnostic, preventive and therapeutic procedures. Infection models and work in the S3 safety laboratory, where research can be conducted using the active SARS-CoV-2 virus, form a focus here.

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BEAT-COVID – Built-up Existing and Advanced Therapy strategies against COVID-19

The corona pandemic highlights the need to prepare against emerging pandemic-spreading infections by establishing platform technologies for the rapid development of new antiviral strategies. Advanced Therapy Medicinal Products (ATMPs), especially those based on genes, are particularly interesting and are promising therapies for infectious diseases. As a platform technology, they can be used not only in the context of the current pandemic against SARS-CoV-2, but also against future, currently unknown pathogens in a very targeted manner against respective virus-specific targets. The further development of highly specific inhalable antibodies for the regulation of the excessive immune response in lung failure also represents promising therapeutic approaches.

The project consortium focuses on novel therapies for the treatment of COVID-19 in particular and infectious diseases in general. The team will develop novel therapeutic strategies to inhibit the entry of SARS-CoV-2 into respiratory epithelial cells. These could be used to reduce viral replication to prevent COVID-19 disease. Another project goal is the development of a therapy to inhibit the excessive immune response of COVID-19 by inhalation of anti-inflammatory antibodies. Fraunhofer IZI contributes to the project with its long-standing expertise in terms of production and preclinical evaluation of ATMPs, biomolecules and vaccines. The departments Preclinical Development and Validation, GMP Process Development / ATMP Design as well as Vaccines and Infection Models are involved in the project.

Partners
Fraunhofer Institute for Toxicology and Experimental Medicine ITEM (Coordination), Fraunhofer Translational Center for Regenerative Therapies TLZ-RT at the Fraunhofer Institute for Silicate Research ISC, Fraunhofer Institute for Applied Polymer Research IAP, Fraunhofer Institute for Reliability and Microintegration IZM

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C19 lung chip – Drug repurposing using a COVID-19 infection model in an immunocompetent lung-on-chip platform

Organ-on-chip platforms integrate complex tissues in a micro-physiological environment with the aim of simulating human biology outside the human body and even integrating aspects of the human immune system. The C19 lung chip project combines the skills and know-how of the Fraunhofer Institute for Interface Engineering and Biotechnology IGB in using organ-on-chip platforms for pharmaceutical studies with the expertise of the Fraunhofer Institute for Cell Therapy and Immunology IZI in infection models as well as its existing experience with the SARS-CoV-2 virus. The Immunology department has the only safety level 3 laboratory within the Fraunhofer community. This constitutes a precondition for working with highly pathogenic viruses, such as the SARS-CoV-2 virus.

At present, there are hopes of finding a treatment for COVID-19 infections through drug repurposing, i.e. the use (of combinations) of approved drugs. A number of possible candidate drugs have already been identified in various studies and there already are (more or less substantiated) reports regarding successful treatment for some of these.

In the framework of the C19 lung chip project, the scientists want to carry out non-clinical studies with the help of a lung model system. This helps to significantly speed up the first explorations as to the effectiveness of certain

substances in the fight against SARS-CoV-2, compared with conventional methods, such as the use of animal models. Furthermore, the organ-on-chip technology is also supported by the fact that the current exceptional situation and the extreme strain on the healthcare systems make the execution of extensive and protracted clinical studies for a large number of possible therapeutics very difficult. Therefore, methods for the fast, resource-saving pre-clinical validation of possible candidate substances are very helpful. Against this backdrop, the C19 lung chip project initially aims to establish a COVID 19 lung infection model which simulates the pathogenesis of COVID-19. As a second step, this model is then to be used to test the effectiveness of up to 40 different substances or substance combinations.

Partners
Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB (project lead), Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Divison Molecular Biotechnology

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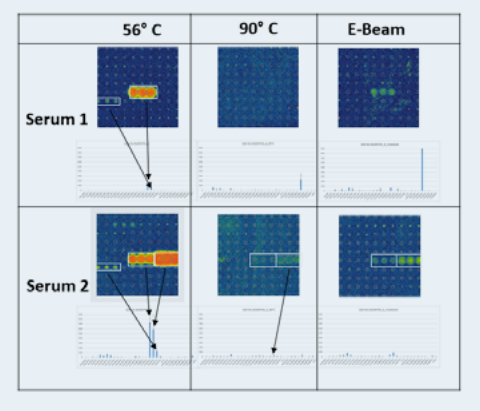
CoV-tot – Examination of the influence of virus inactivation on the epitope spectrum in (COVID-19) serums

At present, serological diagnostics for COVID-19 are only offered based on proteins. In addition, to unexpected false positives, clinical diagnostics specifically report problems with previous infections with related Corona viruses. This is because the recognition sites of the patients' antibodies (epitopes) are only partly specific to SARS-CoV-2, while others are found in many related Corona viruses.

Therefore, in future, serological tests will also have to be developed on the basis of defined epitopes of SARS-CoV-2 or other Corona viruses which permit both simple and highly individualized diagnostics with the help of different specific and ubiquitous epitopes. The Ligand Development Unit at Fraunhofer IZI has comprehensive experience in identifying epitopes directly from serums. It is already evident that SARS-CoV-2 infections lead to a strongly personalized immune response which is shaped by previous Corona infections.



The signal of antibodies against different epitopes in the peptide array is individually and significantly reduced through pretreatment. Some of the antibodies can no longer be detected and are probably destroyed by the application of an inactivation method.

However, in all diagnostic activities, the serums obtained from infected patients are pre-treated to inactivate the virus before the serums can be used in testing. In the context of CoV-tot, it was demonstrated that different methods for virus inactivation have a very different influence on different antibodies in the sera. This can lead to very different results in serological tests in individual cases. Furthermore, the studies have shown that a slight denaturation of the sample seems to remove the blocking of individual antibodies by unknown serum components. Thus, better results can be obtained.

Two methods of viral inactivation have been identified as suitable, firstly heating to 56 degrees Celsius for ten minutes for liquid samples and secondly treatment with 70 % ethanol when antibodies are immobilized on protein A.

The knowledge gained in CoV-tot is a starting point to explore differences in disease progression also in the context of clinical trials for drug treatment of COVID-19.

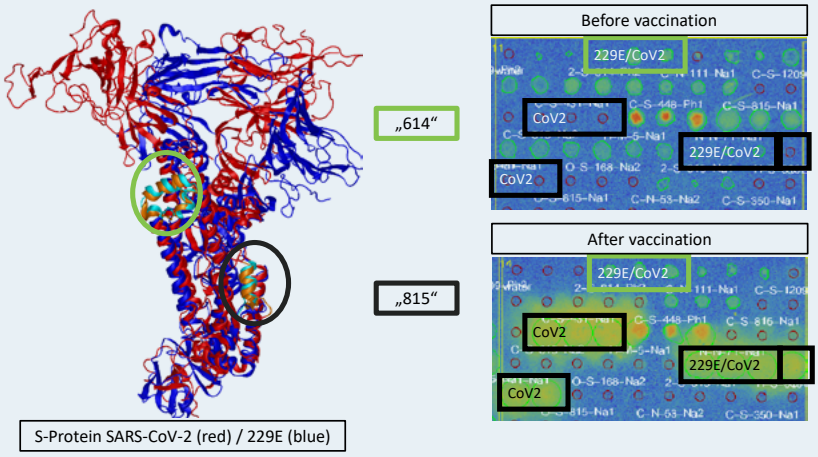
Partner
Klinikum St. Georg, Leipzig, Germany

EpiCoV2020 – SARS-CoV-2 specific serological diagnostics based on epitopes

Coronaviruses have accompanied mammals for a very long time. At least four different endemic corona viruses are circulating in humans and have left an imprint on the immune system. Therefore, this project aimed not only at identifying epitopes recognized by antibodies after SARS-CoV-2 infection, but also, the endemic relatives. By applying the epitope fingerprinting technology developed in this working group, even the small differences in amino acid sequences of highly similar viral proteins can be observed. The analysis identified SARS-CoV-2-specific epitopes, and also epitopes recognized by very similar antibodies in three patient groups: patients with respiratory infections before 2020, COVID-19 patients and vaccinated patients. A large number of peptide epitopes were printed as arrays on slides, and tested using more than 1000 serum samples. The quantity of serum antibodies bound to peptide spots could be recorded and analysed easily with the help of fluorescence labelling, followed by scanning in the laser scanner, and using a new, robust automated analysis of the images generated. This new image analysis system was developed in the framework of the project. It was thanks to this development that such a large number of measurements could be analysed quickly and reliably.

By correlating the results from the previously mentioned three patient groups, large varieties of antibodies against the S-protein and RNA-polymerase were identified, originating from previous infections with endemic strains. Some antibodies circulate in serum already before the vaccine or immediately after SARS-CoV-2 infection. Surprisingly, some cross-reactive antibodies recognize also epitopes in S-protein, with highly identical structure despite their distinct amino acid sequences (Fig. 1).

In future, these and other epitopes can help to track specific individual antibodies rather than tracking antibodies on a protein globally. This would permit tracking of the individually very diverse immune responses to COVID-19 and other vaccines.



On the left, Figure 1 shows the superimposed structures of the S proteins of SARS-CoV-2 and the endemic corona virus 229E. Two very similar areas generating cross-reactive antibodies are marked in green and black. The correlating peptide epitope spots are outlined on the right side in a peptide array image. This shows the results from a patient before and after vaccination. In this case, there is probably an existing immune response to the 229E corona virus, since SARS-CoV-2-specific as well as cross-reactive antibodies developed after the vaccination.

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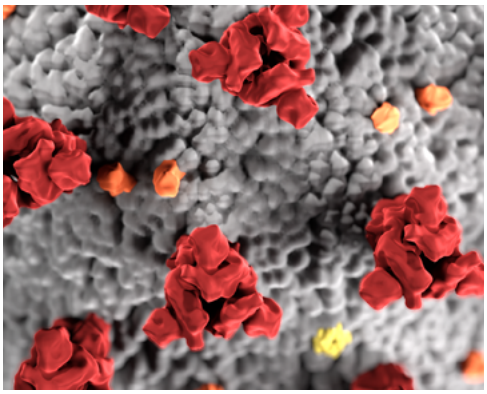
CoronaSense – COVID-19 peptide binding analysis for diagnostics and treatment

Knowledge of the sites at which the virus binds to its host cell and understanding its binding behaviour are of fundamental importance for designing active ingredients that can stop the binding process and also for the development of diagnostic tests based on such binding. The SARS-CoV-2 virus has many spike proteins on its surface; each of which has three geometrically precise binding sites. Therefore, binding can occur at several binding ligands, such as peptides, provided the densities of the DNA levers and the peptide numbers are adjusted to it. Compared with the affinity of the first binding, every further binding leads to a significant increase in affinity. This has already been proven in influenza viruses by the Bioanalytics and Bioprocesses Branch of the Fraunhofer Institute for Cell Therapy and Immunology.

In line with this, multivalent binding partners constitute a promising option for the inhibition of viruses on the host cell. The SwitchSense technology was modified in the CoronaSense project to adjust it to the investigation of multivalent bindings. This was used to analyse: (1) recombinant SARS-CoV-2 spike proteins, (2) complete SARS-CoV-2 viruses and (3) pseudo viruses expressing the SARS-CoV-2 spike protein. Moreover, the viruses were sized using dynamic light scattering. This is a further measuring parameter for characterising a virus sample in terms of its homogeneity and another differentiating factor in the identification of different viruses. CoronaSense could prove that variations in the spike protein lead to a change in the binding behaviour. This might have an effect on the infectiousness and virulence of the SARS-CoV-2 virus versions. Further research work by the CoronaSense team is intended to broaden these insights.

The invention of a nano-structure with a nucleic acid scaffold and virus-binding peptide moieties (patent: WO2018215660A1) of the DNA Nanodevices Unit was used for diagnostic purposes in the framework of CoronaSense.

Partners
Branch of Bioanalytics and Bioprocesses at the Fraunhofer Institute for Cell Therapy and Immunology IZI, Dynamic Biosensors GmbH, PSL Peptide Specialty Laboratories GmbH



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CoroVacc – Development of a Sars-CoV-2-specific vaccine based on Herpes viruses

Over recent decades, vaccines, which are by far the most effective preventative measure against infectious diseases, have contributed decisively to the reduction of illnesses and even the eradication of pathogens. Vaccines based on attenuated viruses, in particular, are highly effective since they induce both aspects of the immune response – on the one hand, the humoral aspect through the production of pathogen-specific antibodies and, on the other hand, the cellular aspects through the T cell-mediated immune response.

The Corona pandemic is highlighting the fundamental importance of the fast development of effective vaccines for new pathogens. In the framework of the CoroVacc project, a Sars-CoV-2-specific vaccine virus based on an established platform vector (herpes virus derivative) should be developed.

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The developed platform technology can quickly adapt the herpes virus vectors on a modular basis. The HSV-based vaccines were initially evaluated for the growth and expression of the SARS-CoV-2 epitopes. As a next step, immunization will be analysed.

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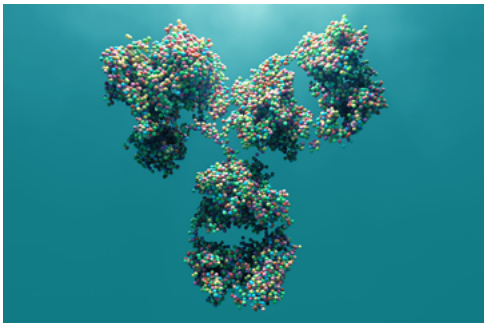
CoVER-Ab – Human antibodies against SARS-CoV-2 for COVID-19 prevention and treatment

In the framework of the CoVER-Ab project, human monoclonal and neutralising antibodies against SARS-CoV-2 are to be extracted initially. These antibodies are then checked for their anti-viral effectiveness in cell cultures and a selection of these is then examined for effectiveness and safety in a transgenic mouse model and a rhesus monkey model.



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The Preclinical Validation Unit has established the infection model with human ACE-2 transgenic mice. Various doses of SARS-CoV-2 were used for this. During subsequent efficacy and safety testing, the neutralising antibodies were administered either before (prophylaxis) or after (therapy) the infection. It has been shown that these neutralising antibodies substantially reduced virus replication. The data were published in the European Journal of Immunology: Peter AS, Roth E, Schulz SR, et al. A pair of noncompeting neutralizing human monoclonal antibodies protecting from disease in a SARS-CoV-2 infection model. Eur. J. Immunol. (2022). doi: 10.1002/eji.202149374

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DEFEND-CoV2 – Testing of vaccines and active agents against SARS-CoV-2

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In the framework of the DEFEND-CoV2 project, an infrastructure for testing and evaluating vaccines and active agents against SARS-CoV-2 is to be created with the aim of giving, in particular, smaller companies and academic institutions without S3 resources, the possibility to quickly test their candidates and to validate these in comparison with other technologies. At the same time, Fraunhofer's own efforts to develop vaccines and active agents are being promoted. In this process, the focus is on proprietary vaccine candidates consisting of inactivated pathogens, nucleic acids and vector vaccines. In this context, (intranasal) application through the airways is considered as an important method since a local and, therefore, potent effectiveness can be established at the virus's point of entry.

In order to be ready for the current as well as for future virus pandemics, the Department of Vaccines and Infection Models and the Department of GMP Process Development / ATMP Design of the Fraunhofer Institute for Cell Therapy and Immunology IZI are working to build a vaccine and active agent pipeline in the DEFEND-CoV2 project. This should also facilitate fast production for preclinical testing and the further clinical development under GMP (Good Manufacturing Practice). As a result, developers can be offered the entire value chain from preclinical testing to the production of the first clinical test specimen. This is particularly important for fast tracking as demanded by the World Health Organisation (WHO) for pandemics.

disCoVer 21 – Highly sensitive lateral flow systems for the detection of viral pathogens

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Lateral flow strips have provided an easy-to-use platform for users to detect various biomarkers (to detect a pregnancy or Covid-19), environmental pollutants or food contaminants. DisCoVer21 uses this basic technology to develop a quick test for detecting SARS-CoV-2-RNA without a PCR test. This would eliminate lengthy analysis steps (transcription of RNA into DNA and subsequent PCR), which sometimes lead to long waiting times for a smear result.

Due to a shortened analysis time, infected persons can be identified, isolated and treated more quickly if necessary. At the same time, chains of infection can be better traced in order to further reduce the spread of the virus.

To simplify sample analysis and increase throughput in laboratories, disCoVer 21 targets highly sensitive lateral flow test strips on which the target substances are directly and specifically detected. In addition, this project permitted the development of competences for the in-house production and optimization of lateral flow strips. This is already being used and expanded on in various projects for detecting infectious agents. Detection methods which are more sensitive than the conventional gold nanoparticles are offered to industrial and project partners. As a result, the project has created a sustainable basis for future projects.

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DRECOR – Drug repurposing for Corona

The World Health Organisation (WHO) has declared the corona virus epidemic an international health emergency. Vaccines and drugs for the prevention and management of the new corona virus are still urgently needed. The fastest route to an effective therapeutic agent would be using an existing drug approved for other indications. The DRECOR project team uses this drug repurposing approach.

The project partners aim at generating candidate molecules formulated for inhalative administration or systemic administration targeting the airways. This has been implemented successfully. Moreover, a prototype device has been created for clinical development. Moreover, the DRECOR team will provide sophisticated models and test systems that can be applied to other projects and indication areas. Fraunhofer IZI will contribute its expertise in the in vivo efficacy testing of suitable drug candidates.

Partners
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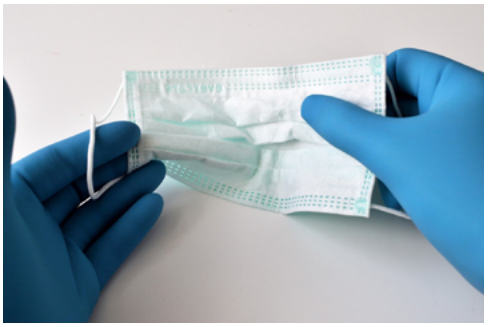
SENSE-CoV2 – Analysis of the innate immune recognition of SARS-CoV-2 using recombinant viruses

Containment of the corona pandemic is hampered by a significant proportion of infected persons showing very few or no symptoms. The fact that SARS-CoV-2 is able to multiply without signs of inflammation suggests that innate immune control against SARS-CoV-2 may be deregulated and less effective.

Within the framework of the SENSE-CoV2 project the research team aims to characterize mechanisms that enable SARS-CoV-2 to escape detection by the human innate immune system.

The identification of viral proteins that prevent early immune control and their characterization in infection experiments will provide important foundations and new target structures for a possible development of antiviral drugs aiming at improved control of the virus by the innate immune system.



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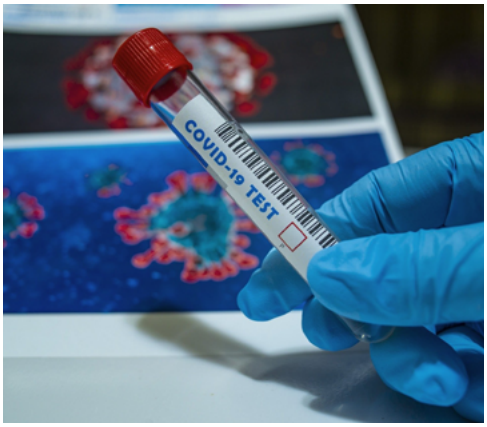
The measure is co-financed with tax funds on the basis of the budget approved by the Saxon State Parliament.

SaxoCOV – Saxon COVID-19 research consortium

The consortium conducts a Saxony-wide field study on the spread of SARS-CoV-2. It is supported by two further, non-Saxon research institutes. The aim is to create a scientific instrument to follow the development of the SARS-CoV-2 epidemic in the German Free State of Saxony on multiple levels. The field study will on the one hand serve to monitor the effectiveness of governmental measures to contain the pandemic and on the other hand support the detection and limitation of outbreak scenarios.

The samples and data collected in the field study will also be used in an accompanying research study to answer further research questions. In particular, the question is pressing as to which causes are responsible for the very different mild or aggressive course of the disease and whether there are parameters with which these different courses can be predicted.

Moreover, the research consortium reached out to all people in Saxony in several anonymous online surveys. The scientists and researchers wanted to use the experience and assessments of the population to find out more about routes of transmission, the effectiveness of the measures during the pandemic and the impact of the pandemic on the people. Saxon pupils and teachers were initially surveyed from early November 2021 to the end of the year. Thereafter, from December 2021 to March 2022, a Saxony-wide survey of the population was carried



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out. The project team will now model, e.g., the spread of infection and draw conclusions regarding the perception of the effectiveness of measures on the basis of the data collected.

Partners
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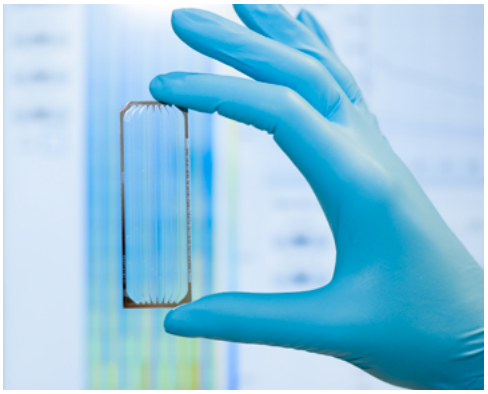
www.saxocov.de (in German only)

SARS-CoV-2 whole genome sequencing according to coronavirus surveillance regulation

The worldwide spread of SARS-CoV-2 (Severe acute respiratory syndrome coronavirus type 2) as well as new virus variants with putative increased risk of infection make a timely determination of the currently circulating virus strains necessary. With the aim to increase the number of SARS-CoV-2 genome sequencing in Germany and thus to detect the spread of the virus as well as the emergence of new variants at an early stage, the Coronavirus Surveillance Ordinance (CorSurV) came into force on 19 January 2021. This regulation requires that at least 5 % of all samples tested positive for SARS-CoV-2 must be sequenced (10 % if there are fewer than 70,000 new infections in a week nationwide). In addition, all sequencing data obtained must be transmitted to the RKI via the DESH platform and the findings must be reported to the "Gesundheitsämter" in order to collect all data centrally.

To perform whole genome sequencing, an approach is used in which the complete viral genome is first amplified in sections, using specific PCR reactions. Subsequently, these genome sections are labeled with sample-specific barcodes as well as sequencing adapters. This allows multiple samples to be sequenced in parallel, i.e. the sequence of nucleic acid bases of each viral genome is determined. The resulting raw sequence data is subjected to bioinformatics analysis, in which the nucleic acid sequences of the individual genome segments are assigned to the corresponding samples and reassembled into a complete viral genome. Subsequently, the sequenced viral genome is aligned with the reference genome of the SARS-CoV-2 strain originally encountered in Wuhan. If



To sequence them, the samples are applied to a FlowCell (shown in the image) and analysed afterwards.

relevant changes are detected compared to the reference genome, the new viral sequence is checked against a database to determine which viral variant it is. The results are compiled in a report and sent to the respective client (clinical partners or diagnostic laboratories), and the complete sequence data is transmitted electronically to the RKI.

Knowledge of the predominant virus variants, combined with information on the timing, frequency and location of occurrence, enables the determination of changes with regard to the speed of spread and severity of the disease caused and, if necessary, the initiation of appropriate measures by the relevant authorities.

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Anti-tumor activity effectively mediated by car macrophages

The launch of the first programmed killer cells (chimeric antigen receptor (CAR)-carrying T cells; product name "Kymriah" from Novartis AG) has significantly expanded the therapeutic options for blood cancer patients. However, the use of CAR-modified T cells, due to their biological properties, remains below expectations, especially in the treatment of solid tumors. This is mainly due to the fact that the therapeutic cells are often not able to penetrate into the tumor mass. In this context, it is known that the tumor environment (the so-called microenvironment) inhibits the activity of programmed killer cells. To actively address these challenges, the suitability of different starting cells for developing new cell and gene therapeutics will be tested. In this project, CAR macrophages will be used to generate and implement a new cellular therapeutic approach against solid tumors that have been difficult to treat so far. For this purpose, macrophages are isolated from human donor material and subsequently equipped with chimeric antigen receptors (CAR) directed against prominent tumor antigens. The ability of the CAR macrophages to target tumor cells is expected to be maximized by inducing and locally releasing type I interferons (type1 IFNe). In addition, macrophages are expected to reprogram the tumorigenic milieu of the solid tumor into an anti-tumorigenic milieu to force tumor growth arrest while sensitizing tumor cells to standard therapies. According to their biological function, macrophages can further: 1. actively phagocytize tumor cells and 2. present tumor-specific antigens, which in turn activate other immune cells to fight the tumor.

The use of CAR macrophages can greatly expand therapeutic options for various types of tumors. Unlike expensive, patient-specific cell therapeutics, macrophages can also be used and applied from foreign donors (as an allogeneic product). In particular, transport routes and times can be reduced and the availability of therapies for affected patients can be increased enormously.

The project is characterized by its translational character, since not only the conceptual and technical feasibility of CAR macrophages in a biological context will be addressed, but also a standardization of CAR macrophage production with the help of appropriate protocols will be secured and described.

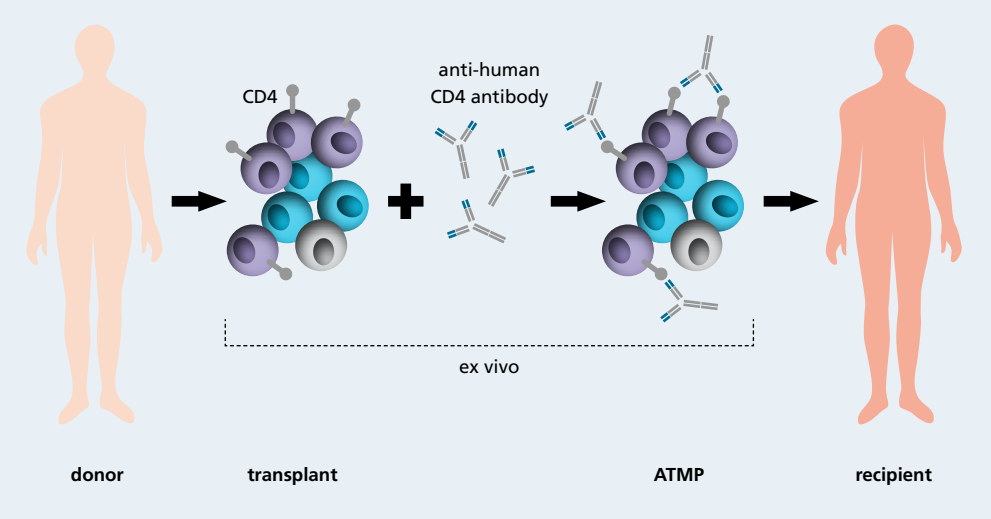
Preclinical development of an advanced therapy medicinal product (ATMP, Palintra®) to prevent the graft-versus-host disease (GvHD)

With an incidence of 30 to 40 percent, the graft-versus-host disease (GvHD) is one of the main complications after an allogenic haematopoietic cell transplant. Conventional treatment methods aim for an unspecific suppression of the entire immune system, which can significantly increase the risk of infections and relapses. Moreover, the long-term success to be expected might be low and associated with both hepato- and nephrotoxic side effects. As a result, the development of less straining alternative treatments is urgently needed.

The GMP process development / ATMP design department is developing protocols and methods to prepare the production of the advanced therapy medicinal product (ATMP) Palintra® to prevent GvHD under GMP conditions. Pre-incubation of a haematopoietic cell transplant with an anti-human CD4 antibody reduces undesired immune responses against the host tissue after transplantation. However, the graft-versus-tumour (GvL) effect which protects against relapses is maintained.

As part of the pre-clinical development phase, cell-based functional assays are established. These potency assays can measure the function of the immunotolerance-inducing, anti-human CD-4 antibody in vitro for the first time ever. Moreover, next generation sequencing is to be used to detect changes in the transcriptome of T cells and to draw conclusions regarding the molecular effect of the antibody. Additionally, the treatment efficiency of Palintra® in GvHD prevention is examined in vivo and compared with conventional therapies.

In addition to fulfilling official pre-clinical requirements, the experiments listed above can generate new insights into immunological processes in inducing immunotolerance and into GvHD. These models and insights are particularly important not only for haematopoietic cell transplants, e.g., in leukaemia treatment but also for stem cell transplants for other indications (e.g. autoimmune diseases).



Ex vivo treatment of a haematopoietic cell transplant with the anti-human CD4 antibody Palixizumab® to produce the ATMP Palintra®.

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T-Charge

CAR-T cell therapy is a cancer immunotherapy. It uses the patient's own T cells to fight certain types of cancer. To do this, the cells are harvested in the clinic by leukapheresis and genetically reprogrammed in vitro to recognize cancer cells that carry a specific antigen on the cell surface by means of a chimeric antigen receptor. After lymphodepleting chemo-therapy, the reprogrammed cells are infused into the patient, where they can proliferate and start the immune response. In August 2017, Kymriah® (CTL019 / tisagenlecleucel), the first CAR (chimeric antigen receptor) -T cell therapy, became available in the US. Kymriah® received FDA approval for children and young adults up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) who have not responded or have already relapsed to usual therapies, and in May 2018 for adult patients with diffuse large B-cell lymphoma (DLBCL) who have relapsed or not responded to therapies after two or more lines of systemic therapy. In August 2018, Novartis announced the approval of the EU Commission for these two indications following a corresponding recommendation by the European Medicines Agency (EMA). Fraunhofer IZI has been a manufacturing site for this CAR-T cell therapy in Europe for several years and in 2021 handed over the long-standing very successful collaboration with Novartis regarding the manufacture of CTL019/Kymriah® in accordance with the contract. Personnel experienced in the manufacturing and quality control of CTL019/ Kymriah® are now handling the process transfer and manufacturing of novel "next generation" CAR-T investigational products developed by Novartis. This T-Charge™ program was first presented by Novartis in December 2021 at the 63rd American Society of Hematology Annual Meeting (ASH). The T-Charge™ platform preserves T-cell stemness (the ability of T cells to self-renew and mature), an important property of T cells that is closely linked to their therapeutic potential. This results in a product with greater proliferation potential and fewer exhausted T cells. With T-Charge™, CAR T cell expansion occurs primarily in the patient's body (in vivo), eliminating the need for extended culture time outside the body (ex vivo). Beside those changes in the cells' biology, the T-Charge platform will be faster and more reliable compared to traditional CAR-T technology by simplifying processes and optimizing quality control.

Preparatory work for production in clean room class A.

PoC-Initiative ROR1 CAR-T

In 2017 and 2018 respectively, the US FDA and the European Commission approved the first CAR cell therapy. This was the first time a gene therapy was approved for cancer treatment. This revolutionary treatment form is also the focus of the ROR1 CAR T research project. The chimeric antigen receptor (CAR) developed at Würzburg University Hospital recognises the ROR1 molecule, which is, e.g., expressed by cancer cells in leukaemia as well as breast and lung cancer.

The patient's own cells are collected using leukapheresis to produce the cell product. Afterwards, T helper cells and cytotoxic T cells are selected by magnetic cell separation. The genetic material for the CAR is transferred into the T cell genome by non-viral gene transfer with help of the "Sleeping Beauty" transposon system (jumping gene). This re-programmes the T cells so that they recognise ROR1-positive cancer cells as being "foreign" and kill these by releasing cytotoxic messenger substances. The reprogrammed cells are in vitro expanded and intravenously administered to the patient.

CliniMACS Plus device for T-cell selection.

This project is sponsored as a pilot project by the Proof-of-Concept Initiative, which was established by Fraunhofer Society, Helmholtz Association and the Association of German Medical Faculties to promote the translation of innovative research projects. This funding was used to prepare pre-clinical studies on the safety and effectiveness of ROR1 CAR T cells; moreover, the clinical translation into a phase I/II study (first-in-man study) is to be prepared.

In this project, test batches were initially produced. These were then used to optimise the process with regard to the demanding production under GMP conditions and qualify the required equipment. After the successful establishment of the process and the required specifications, three successful validation batches were produced under cleanroom conditions and the analytical methods were established. Moreover, the cell products generated with these validation batches were used to validate the analytical methods relevant for microbiological safety (mycoplasma, sterility, bacterial endotoxins) and to commence the validation of the proof of genomic safety (determination of vector copy number). Following the conclusion of these validations, an application for the inclusion of the investigational medicinal product in the existing production authorization according to section 13 of the German Drug Act is to be submitted to the competent authority.

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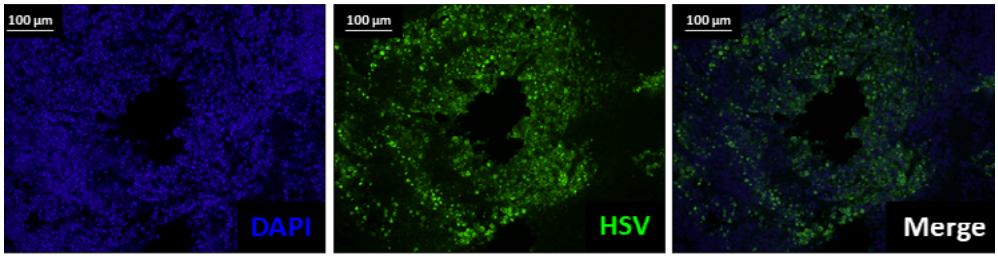
TheraVision – platform technology for the development, production and testing of oncolytic herpes simplex viruses for tumor therapy of lung cancer

Viruses are able to penetrate cells and produce both foreign and viral proteins. Afterwards they multiply in order to kill the infected cells. Due to the fact that oncolytic (cancer-destroying) viruses selectively kill tumor cells, they have become an emerging hope in cancer therapy. The Herpes Simplex Virus (HSV) is one of those viruses.

We aimed to increase the efficacy of the oncolytic activity of an HSV-1 based vector by genetically introducing different genes for immune modulation and for targeting the optimization of tumor therapy. Thus, the virus-mediated oncolysis is combined with immunotherapy in one virus vector and an effective destruction of tumors as well as metastases is possible. The objective of the project "TheraVision" is to establish a broadly applicable platform technology based on HSV for combinatorial oncolytic virus immunotherapy.

As a proof of concept, an oncolytic virus was developed for the therapy of non-small cell lung cancer (NSCLC), whereby the Fraunhofer IZI established the appropriate mouse model. The cells of the lung cancer tumors express the reporter Firefly-Luciferase in order to be detected by a highly sensitive light camera in vivo. The tumors showed a significant increase in bioluminescence intensity, which directly corresponds with an increase in size. The treatment of these tumors with an attenuated and neurotoxicity-deleted HSV vector led to a significant reduction in tumor growth and bioluminescence intensity compared to an untreated control group. Furthermore, the attenuated vector with deleted neurotoxicity genes caused a significant reduction of the viral load in the brain in comparison to an unmodified HSV vector.

To analyze the immunotherapeutic activity of novel functionalized oncolytic viruses, this tumor model must still be transferred into humanized mice with the appropriate human tumor in an allogenic immune environment that mimics more the natural situation. Finally, a broadly applicable platform technology to test the efficacy of virus vector and immune therapies or combinations will be available for future endeavors.



HSV-induced plaque formation in tumor tissue sections of mice after intratumoral virus therapy. DAPI (blue) depicts the cell nucleus and HSV (green) the viral proteins in infected lung cancer cells.

Infection pathology

Efficacy of novel helicase-primase based therapy for human Herpes Simplex Virus (HSV)

Currently, human Herpes Simplex Virus (HSV) infection affects about 82 % of Germany's population. The pathogen is categorized into two types, which differ in their predilection for the site of infection. HSV type 1 (HSV-1) is associated with a wide range of clinical manifestations including cold sores. In contrast, HSV type 2 (HSV-2) is linked to genital herpes. Both types are able to develop severe disease progression leading to fatal Herpes Simplex Encephalitis (inflammation of the brain).

Until now nucleoside analogues, such as Acyclovir and Valacyclovir, are still the treatment of choice for HSV infections. However, due to the existence of nucleoside-resistant viral strains alternative therapies are needed. Recently, this alternative has been represented by helicase-primase inhibitors (HPIs), which use a novel mechanism of action to inhibit viral replication. In a drug development trial we analyzed the antiviral efficacy of new drug candidates for the treatment of HSV infections in a mouse model.

Despite the lower dose, a better outcome in clinical parameters using HPI therapy in comparison to Valacyclovir control was observed. Toxic side effects were not detected during the monitoring period of 3 weeks post infection. The subsequent analysis showed that treated animals harbor a significantly lower viral load compared with placebo animals.

This project showed that treatment with the new HPI candidates can significantly reduce or prevent clinical symptoms. HPI's are at least one order of magnitude more potent and efficacious compared to Valacyclovir. Thus, candidates of the new drug class are promising inhibitors of HSV infections in vivo and should be translated into clinical trials.

https://www.science.org/doi/abs/10.1126/scitranslmed.abf8668

https://www.sciencedirect.com/science/article/pii/S0166354221001807

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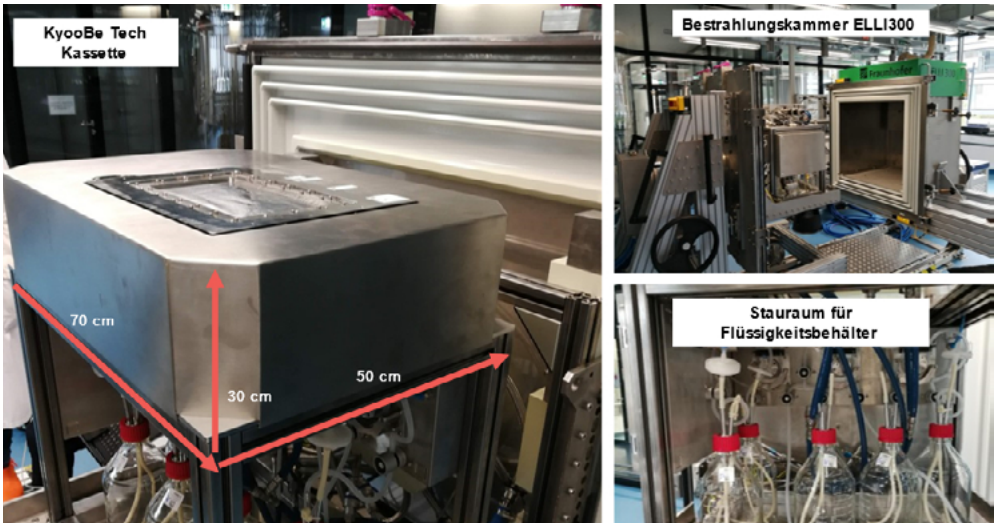
Electronbeam-based inactivation of viruses and bacteria – the way to the market

For decades, the production of dead vaccines has been based on killing pathogens by chemicals. Although this method is used for a number of vaccines, it harbors some problems. The chemicals used, such as formaldehyde, are harmful to the environment and health and must be removed before a vaccine can be made from it. In addition, the inactivation process often takes several days to weeks. Since 2014, therefore, together with the Fraunhofer Institutes IPA and FEP, an approach has been pursued that makes the use of harmful chemicals unnecessary and inactivates the pathogens within milliseconds. For this solution, the team received the Fraunhofer Prize "Technology for People and their Environment" in 2021. Already in 2019, the technology was out-licensed to the filling line manufacturer Bausch & Ströbel, from which the company KyooBe Tech GmbH emerged as a spin-off, which will take over the further development until marketability at the end of 2023.

In 2021, a joint consortium tested concepts and performed test runs that are optimized for manufacturing processes in the pharmaceutical industry. For example, several sensors for different process parameters, e.g. for measuring the temperature, have been integrated. The current cassette prototype is made entirely of pharma-compliant stainless steel. The heart of the cassette is a stainless steel roller over which a thin liquid film is conveyed and irradiated with low-energy electrons via an irradiation window. A scraper system then removes the irradiated liquid from the stainless steel roller and directs it into a separate product container. With the optimized cassette system, between 10 and 20 L/h throughput can currently be produced depending on the type of liquid. This represents an increase of a factor of 10 compared to previous systems. The cassette is also mounted on a carrier module with enough space for various containers and technical equipment.

From 2024, devices should then be commercially available as well as much more compact than the current structure. A device the size of a standard laboratory refrigerator is conceivable. The focus is on the production of vaccines, but an extension to other areas of application such as reducing potential contamination in biological manufacturing processes or producing cell therapeutics is possible.



Overview of the cassette prototype with dimensions (left), as well as the underlying storage space in the carrier module with space for several liquid containers (bottom right) and the integration of both parts into the irradiation chamber of the ELLI 300 irradiation system (top right).

Non-invasive diagnostics by breath analysis

Exhaled air contains substances known as volatile organic compounds (VOCs), which provide information about metabolism. In a variety of diseases, including infections, cancer and neurodegenerative diseases, the metabolism and thus the composition of the exhaled VOCs changes. Detection of these VOCs offers the opportunity to diagnose diseases early and non-invasively.

Ion mobility spectrometry (IMS) can detect VOCs within minutes directly at the point-of-care. The BMBF project "Breath Alert" investigates whether IMS can be used to detect antibiotic resistance in bacteria. In the Fraunhofer-versus-Corona cluster project "M3Infekt", IMS technology was further developed at the Fraunhofer Center for Microelectronic and Optical Systems for Biomedicine (MEOS) with the participation of Fraunhofer IZI. Specifically, methods for sampling via mouth and nose, for short-term sample preservation and for sample preparation were established and tested. At the end of the project, the method was tested on 60 healthy volunteers in two clinical studies in Dresden and Magdeburg. In parallel, a functional novel IMS demonstrator was completed at MEOS. This must now be further developed and optimized in follow-up projects to selectively detect diagnostics-relevant VOCs in complex matrices such as exhaled breath.

Subject test for breath analysis.

In the M3Infekt project, the participating nine Fraunhofer Institutes developed further non-invasive and mobile sensors for recording heart rate, ECG, oxygen saturation, respiratory rate and respiratory volume. Concepts for system integration and flexible interfaces were defined and a multimodal AI framework for cross-sensor data evaluation was developed. In addition, requirements regarding conformity to medical regulatory requirements were developed. The overall vision of the project is a close monitoring of relevant clinical parameters for detecting condition deterioration in infectious diseases also outside of intensive care units via a multimodal, modular and mobile sensor system. During the project it has become apparent that several specific solutions for different sub-applications are more useful than a single overall system and thus the benefit of the project results is even increased.

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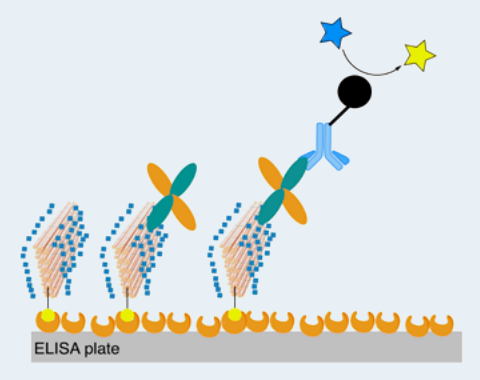
Glyco3Display: DNA-templated assembly of glycans for developing novel pathogen anti-adhesives

Polysaccharides, also known as glycans, are long and complex sugar molecules made up of a chain of monosaccharides such as mannose, glucose or fructose. Numerous glycans are found on the surface of human cells, and are used by disease-causing bacteria or viruses as molecules for recognizing, binding, and eventually infecting the host cells. Therefore, sugar molecules such as mannose, heparin or sialic acid, which are found on the membrane of human cells, are particularly interesting from a medical research perspective. Nanometer-scale geometry also plays an important role here; viruses and bacteria exploit the principles of multivalence, where two or three sugar-binding receptors act cooperatively to more efficiently bind to and infect their targets.

In Glyco3Display, novel carbohydrate-based compounds are created by integrating different glycan molecules with DNA-based structural scaffolds. The approach allows precise arrangements of defined glycan chains with single-nanometer spatial resolution to be established. This brings together two key technologies from the partners Fraunhofer IZI and the Max Planck Institute for Colloids and Interfaces: DNA Nanotechnology and Automated Glycan Synthesis.

One part of this project focuses on creating high-throughput assays for investigating the binding of specific glycan formulations and arrangements to target pathogens or glycan-binding proteins. For this, glycosylated DNA nanostructures have been integrated into two standard, analytical platforms that are widely accessible to researchers around the world.

First, by integrating the DNA-glycan compounds onto microbeads, any standard automated flow cytometry system can be used to quantify the impact that the exact glycan composition and how they are geometrically arranged on DNA scaffolds has on their ability to bind the surface of the pathogen. Alternatively, we different types of DNA-glycan nanostructures with the hardware used for carrying out classical ELISA assays. Thus, synthetic replacements for antibodies used to capture and detect in immune-diagnostics were created. Unlike standard ELISAs or other similar assays, this method allows rapidly screening through many candidate ligands, and additionally controlling the geometric arrangement in which they are presented to targets proteins.



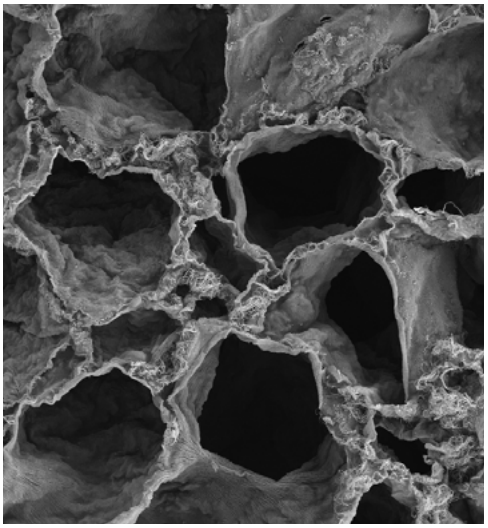
Close to 100 sugar molecules are conjugated to large "DNA origami" nanostructures, formed from several hundred DNA oligonucleotides. When integrated into ELISA plates, these can replace standard antibodies used to capture or recognize targets in immuno-diagnostics.

Further selected projects

Renal tissue models

Today, approx. ten percent of the global population are affected by chronic kidney disease (CKD). The current treatment options comprise dialysis and kidney transplants which, however, are unsatisfactory both medically and in terms of the patients' welfare for several reasons. Therefore, the possibility of a future third option by providing synthetic (bioartificial) kidneys would definitely be very valuable. While impressive progress has been made with research approaches from the field of tissue engineering, the road to functional kidneys seems to be very long. This project aims to establish, primarily, tissue model systems which can be used to address different questions more specifically regarding the efficient decellularization and subsequent recellularization of kidney tissue from rats. After the removal of the animal cells, an extra-cellular matrix (ECM) remains in the form of a delicate, anatomically intact scaffold forming the basis for colonization by human cells. However, both processes – i.e. the removal of the original cells as well as the recolonization with human cells – are complex procedures which can be significantly optimized in certain details. Up to now, perfusion of the organ with chemical reagents has been predominantly used for decellularization. However, this can also lead to a significant impairment of the quality and integrity of the remaining scaffold. For the first time in this project, the application of hydrostatic high pressure treatment (HHD) to the decellularization process is investigated. HHP can lead to a very fast and effective devitalization of the cells so that subsequent perfusion would be shorter and less harmful for the ECM which, in turn, would be very advantageous for recellularization. In addition to intact kidneys, precision-cut kidney sections, which are excellently suited as 3D tissue model systems, are examined in this context.

Finally, this type of tissue model is to be used for a range of questions – from the precise examination of cellular and molecular processes during recellularization, to functional analyses of nephrons and pharmacological issues. The project is sponsored in the framework of the Mecklenburg-Vorpommern state initiative for excellence (HOGEMA consortium). The tissue replacement material research partnership brings together the universities of Rostock and Greifswald as well as Wismar University of Applied Sciences.



] Scanning electron microscope, decellularized organ scaffold. © Electron Microscopy Centre (EMZ), Medical Department of Rostock University

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Fraunhofer Cluster of Excellence Immune-Mediated Diseases – Cell Therapeutics Competence Platform

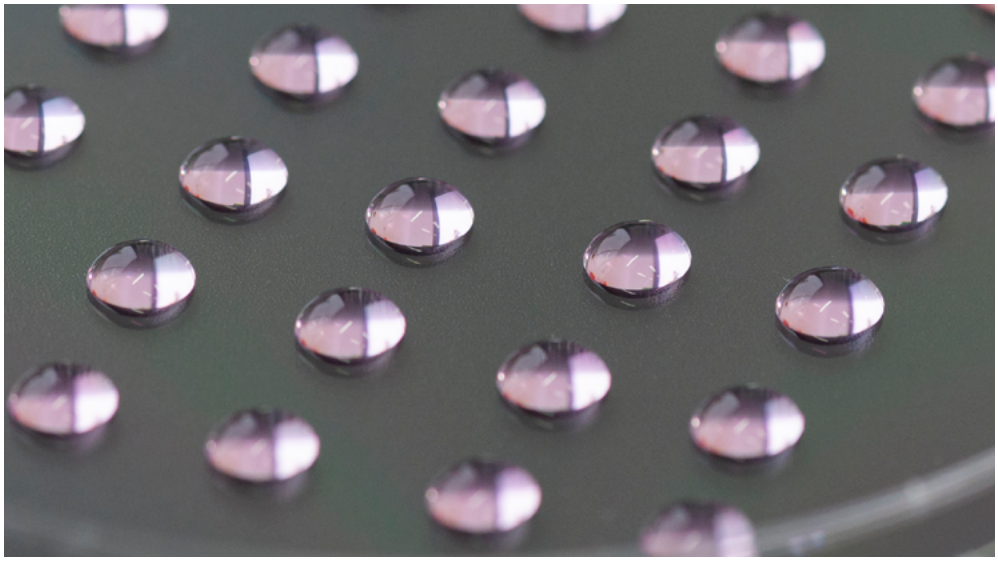
Cell and gene therapies are innovative treatment methods facilitating curative approaches to severe, previously incurable diseases. This includes therapies using genetically modified cells as advanced medicinal products (ATMP). In CAR T cell therapy, the patient's own T cells are modified with chimeric antigen receptors (CAR). Both the approved CAR T cells and the majority of new CAR T cells currently being developed are based on the stable genetic engineering modification of the patient's own cells with the help of viral vectors. However, since the CAR T cell therapy is still a very new method, long-term effects have not been fully studied. Furthermore, persistent CAR T cells partly cause severe side effects. The temporary modification of cells using a messenger RNA (mRNA) coding for the CAR protein constitutes an alternative to the stable version.

The competence platform aims to develop transient CAR cell therapeutics to treat immune-mediated diseases. For this purpose, new mRNA technologies and nano-transporter systems will be developed. As a result, an establishment project is to generate CAR T cells against activated fibroblasts.

Human 3D cell culture and tissue models of fibrosis as well as a novel imaging platform will be used for functional testing. Another goal is to transfer this technology to natural killer (NK) cells to develop donor-independent CAR cell therapies.

Moreover, the platform will be used to develop mRNA-based CAR cell therapeutics with a higher safety profile. This results in a transient ATMP approach to the treatment of fibrotic diseases. To cover the future demand for CAR cell therapies, the transition from autologous products (using the patient's own cells) to allogenic (genetically different) products is supported so that one product batch can be used to treat as many patients as possible.

If the establishment project is successful, further ex vivo models of fibrotic tissues are to be used for CAR cell testing in cooperation with Fraunhofer ITEM. Concurrently, the platform is to be expanded with other cell-therapeutic effects (e.g. T cell receptor-modified cells) and other target indications (e.g. arthrosis) in the medium term.



3D tissue models (hanging drop method) for functional testing of cell therapeutics.

NANOpain - Preclinical models to evaluate the safety of a nanoparticle-conjugated opioid

As part of a joint project funded by the BMBF, a combined drug product for pain relief is being investigated in preclinical studies. The aim is to minimize safety risks prior to first-time use in patients. The NANOpain project is based on a combination of an already approved opioid (preferably kappa-receptor agonist) and a dendritic nanotransport molecule (nanocarrier). According to the EPR effect ("enhanced permeability and retention effect"), the dendritic molecules preferentially accumulate in inflamed and tumorous tissue resulting in a targeted localization and a reduction of side effects such as addiction, aversion and constipation. The efficacy has already been tested by DendroPharm both in vitro and in vivo. At Fraunhofer IZI, the safety-relevant preclinical investigations are carried out in appropriate animal models (small animal model, large animal model) under GLP conditions. First, a pharmacodynamics / pharmacokinetics study is performed in rats to investigate the degradation of the drug as a function of time. The analyses are performed by the GLP testing facility at the Halle site. The toxicological tests of the active ingredient preparation are then implemented in a mouse model as well as in a minipig model. Together with the production of the investigational drug under GMP conditions by DendroPharm, this creates the prerequisite for subsequently testing the developed drug in a Phase I clinical trial at the Fraunhofer Institute for Toxicology and Experimental Medicine. The drug will be tested for safety and tolerability in healthy volunteers in ascending single and multiple doses.

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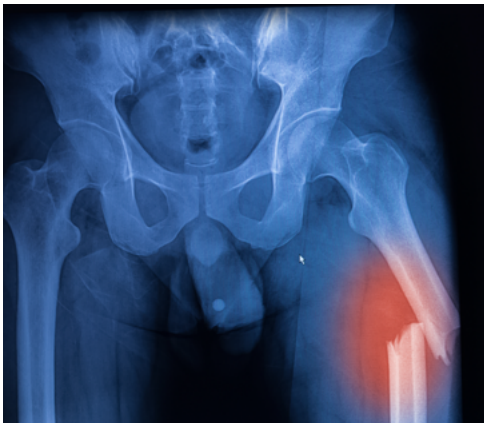
Systems medicine approach for personalized bone defect treatment in patients comorbid with Type-2 diabetes (SyMBoD)

Our bones possess the remarkable feature to heal completely without forming fibrous scar tissue. However, different conditions may lead to a delayed, compromised or absent bone regeneration. Possible reasons could be a critical size fracture or systemic disease conditions, e.g. osteoporosis or type-2 diabetes mellitus (T2DM). In the latter case, tissue revascularization and differentiation of bone forming osteoblasts is often compromised. However, the extent of impaired healing capacities depends on each patient and until now, no diagnostic biomarker exists for prognosis of impaired bone healing before treatment begins. This often increases the burden of patients that suffer from non-healing fractures in standard therapies before a bone implant crafted from inert materials, autografts or allografts is applied. However, those materials are not optimal from different perspectives.

To this end, the SyMBoD projects aims to develop a digital platform for decision-making in treating patients with bone defects suffering from T2DM. This includes (ii) the identification of theranostic biomarkers and (ii) the modeling of individualized, patient- and fracture-specific scaffolds for fracture bridging. Therefore, different tissues (blood plasma and cells, bone tissue and exosomes) from both animal models and human biobanks will be screened in a multi-Omics approach to extract individual molecular profiles. Those profiles will be correlated to further clinical parameters and healing processes by AI-supported bioinformatic methods to stratify patients into risk groups and to identify theranostic biomarkers.

In parallel, bioresorbable polycarpolacton-based scaffolds will be optimized, based on multi-scaling modelling and iterative testing in animal models. This will allow for (i) optimizing biomechanical properties of the material at different size scales and (ii) developing computer models for the prediction of optimal individualized patient- and fracture-specific scaffolds.

Both, molecular and biomechanical models will be implemented into the platform and will guide clinicians (i) to identify risk patients based on selected prognostic biomarkers and (ii) to seamlessly create computer models of individualized scaffolds based on fracture imaging. Finally from those models, real bone implants can be manufactured in a GMP-compliant manner applying CAD-CAM 3-D printing techniques with biocompatible and resorbable materials breaking ground for personalized therapy in bone healing.



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Software development for applications in personalized medicine

Despite a growing number of treatment options, the therapeutic situation for diseases is often unsatisfactory. Personalized medicine can bring fundamental progress through a therapy selection individually adapted to the patient. Computational methods and omic-wide methods are applied to identify and verify new biomarkers for personalized diagnosis and prognosis of diseases. Omic-wide methods are a powerful tool because they allow the simultaneous characterization of a large number of biological markers. Applications even allow to characterize markers at the single cell level or spatially resolved in close proximity to surrounding tissue.

All these methods result in large datasets of high dimensionality, which, combined with clinical follow-up data and machine learning, a sub-area of artificial intelligence, allow tailored therapy choices. With continuous advancements of omic-wide technologies, we expect an increased use in diagnostics and clinical studies. Hence, patient stratification models developed using machine learning methods must meet stringent requirement profiles. In order to address this and to pave the way for using omic-wide diagnostics in immuno-oncology and oncology, software development processes in accordance with the international standard IEC 62304 for medical devices from 2020 to 2021 have been implemented. Such a process landscape in combination with a certified quality management system (ISO9001) allows to develop algorithms for personalized medicine as well as software prototypes for in vitro diagnostics or lab-developed tests.

One example is prostate cancer as the most common malignant tumor indication in men in Europe. Clinical and histopathological risk factors as well as previous biomarkers and their respective classification models inadequately divide the tumors into risk classes. Accordingly, there is a need to improve the risk categorization of prostate cancer. Using next-generation sequencing (NGS), detailed knowledge of the relationship between the activity of molecular signaling pathways and the risk of aggressive disease progression has been obtained [2]. Within "RiboTrend", prototypical software for a classifier for predicting the aggressive disease progression of prostate carcinoma is being developed, which should enable improved tumor categorization.

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European Union

Freistaat Sachsen

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

Sponsors and advisory board

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

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The 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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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.

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