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HIGHLIGHTS AND EVENTS 2019
Events form a key part of the institute’s communication strategy. Fraunhofer IZI once again organized and supported various scientific events and opened its doors to the general public in 2019.

NEW YEAR’S RECEPTION 2019

On January 24, 2019, Fraunhofer IZI came together with the Fraunhofer Center for International Management and Knowledge Economy IMW and biosaxony e. V. to host the New Year’s reception. Around 200 guests were welcomed by Professor Ulrike Köhl and Professor Thorsten Posselt, Director of Fraunhofer IMW, as well as André Hofmann, CEO of biosaxony e. V. Guest speaker Professor Herfried Münkler, political scientist at Humboldt-Universität zu Berlin, held a talk on “Europe’s new geopolitical challenges”. The talk was a parting gift for Fraunhofer IZI founder Professor Frank Emmrich, who stepped back from the institute’s management at the end of 2017 and is an avid reader of Münkler’s work.

POSITIVE EVALUATION OF THE ROSTOCK DEPARTMENT

The Extracorporeal Immunomodulation project group was set up as an off-site department belonging to Fraunhofer IZI in Rostock in March 2011. Since then, the group has focused on the development of new diagnosis and treatment methods in the field of extracorporeal organ replacement systems. An external expert committee positively assessed the off-site department in February 2019 and recommended its permanent integration in the organization. Besides scientific quality and profitability, key criteria of the evaluation included the way in which the group complements other research topics at Fraunhofer IZI, its unique features and how it fits within the Fraunhofer-Gesellschaft. The Fraunhofer-Gesellschaft’s Executive Board and the Bund-Länder Commission (BLK) have followed the recommendation. Since January 1, 2020, the off-site department has been included in the Fraunhofer-Gesellschaft’s regular 90:10 funding, thus safeguarding its future.

GIRLS’ DAY AND BOYS’ DAY 2019 AT FRAUNHOFER IZI IN LEIPZIG AND ROSTOCK

In 2019, Leipzig’s Fraunhofer IZI once again took part in Girls’ Day and even put together a program for Boys’ Day for the very first time. On March 28, 2019, eleven schoolgirls visited the Immune Tolerance Unit and ten schoolboys spent the day at the MicroDiagnostics Unit, where colleagues gave the groups an insight into the workings of a biomedical research institute. The teenagers spent time in the laboratory, where
they isolated plasmid from Escherichia coli and experimented with gel electrophoresis. The Department of Extracorporeal Immunomodulation also participated in Boys’ Day, where six pupils attended the “Washday in the lab” event at the Rostock off-site department. Among other things, they took a closer look at the composition of blood and discovered how it can be tested and analyzed.

SCIENCE CINEMA “CLUB DER ROTEN BÄNDER – WIE ALLES BEGANNN”

As part of the Science Cinema series – an events program organized by Leipzig’s research institutions – Fraunhofer IZI and Leipzig University welcomed attendees to the Forum of Contemporary History Leipzig. The German film “Club der roten Bänder – Wie alles begann” (2019) was played to a full house. The touching film follows six average teenagers whose lives are thrown into disarray from one day to the next. Their daily routines are suddenly shaped by examinations, diagnoses and hospital visits, which is what ultimately brings them together in the “Club of red bracelets”. The podium discussion held after the showing was centered around questions on the current state of cancer research and cancer medicine. Professor Florian Lordick, Director of the University Cancer Center Leipzig, and Fraunhofer IZI Director Professor Ulrike Köhl took part in the podium discussion alongside the film’s director Felix Binder and Tom Hoffmann, who was diagnosed with cancer as a teenager.

SAXONY’S MINISTER PRESIDENT MICHAEL KRETSCHER VISITS FRAUNHOFER IZI

Fraunhofer IZI welcomed Saxony’s Minister President Michael Kretschmer and Novartis Oncology Germany to the institute on June 11, 2019, where Director of Fraunhofer IZI Professor Ulrike Köhl and Managing Director of Novartis Oncology in Germany Heinrich Moisa gave an update on the latest developments regarding new cancer therapies. A joint discussion was then held on the challenges and opportunities facing the region of Saxony when it comes to developing these types of innovative immunotherapies. Novartis and Fraunhofer IZI have been working together in the field of CAR-T cell therapies since 2015. The Leipzig-based Fraunhofer institute is one of the central manufacturing and development sites for the cell therapy Kymriah®. Minister President Kretschmer acknowledged just how important the successful cooperation with the Swiss biotechnology and pharmaceutical company is for Saxony as a business location and encouraged “the start of a strategic dialog between universities, non-university facilities, Fraunhofer and Novartis with a focus on Saxony.”

DG-GT THEME DAY “CAR-T CELLS AND BEYOND”

On September 16 and 17, 2019, 200 distinguished international experts and junior researchers from the field of cell and gene therapy came together at Fraunhofer IZI in Leipzig to talk about the latest developments in immuno-oncology as part of the DG-GT theme day “CAR-T cells and beyond”. As well as discussing current preclinical developments, attendees from the fields of science, medicine and business looked at the latest findings and trends in the manufacture of gene transfer vectors and debated the
progress and outcomes of clinical trials. The spotlight was placed on ethical and regulatory aspects linked to the novel immunotherapies.

**EXPERT ROUND TABLE: “ONE YEAR OF CAR-T CELL THERAPY IN GERMANY”**

One year of hands-on experience with the innovative CAR-T cell therapy in Germany – Novartis and Fraunhofer IZI marked this milestone by inviting journalists and media representatives to an expert roundtable. Since August 27, 2018, patients with certain types of life-threatening blood cancer and extremely limited survival prospects have had the opportunity, for the very first time, to prolong their lives thanks to the CAR-T cell therapy developed by Novartis. In Germany, more than 15 hospitals (effective September 2019) are now certified to carry out this treatment. Novartis has worked closely together with Fraunhofer IZI to establish a complex manufacturing process for CAR-T cells.

**FRAUNHOFER MEOS SHOWCASES ITS WORK AT THE LONG NIGHT OF THE SCIENCES IN ERFURT**

Erfurt opened its doors for the “Long Night of the Sciences” on November 8, 2019. The Fraunhofer project center Microelectronic and Optical Systems for Biomedicine MEOS took part in the program for the first time. The project center brings together Fraunhofer IZI with the Fraunhofer Institutes for Photonic Microsystems IPMS and for Applied Optics and Precision Engineering IOF. Besides listening to talks on the use and continued development of key technologies such as biosciences, microelectronics, optics and photonics for biomedical applications, interested guests were also able to look around various research stations, where they could have a go at microscoping, try their luck at a Petri dish quiz and make their own non-Newtonian fluid.

**IMSAVAR KICK-OFF MEETING**

On December 2, 2019, the interdisciplinary consortium imSAVAR came together to hold its kick-off meeting at Fraunhofer IZI. The consortium boasts 28 international partners from eleven nations under the scientific coordination of Fraunhofer IZI, with Novartis representing the industry partners. As part of imSAVAR (Immune Safety Avatar: nonclinical mimicking of the immune system effects of immunomodulatory therapies), innovative model systems are to be developed for the evaluation of immunomodulatory therapeutic agents. The project will receive a total of 11 million euros in funding from the European Union (GA no. 853988) and will run for a period of six years. The industry partners are matching the funding amount for the project.

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1 *Kick-off meeting for EU project imSAVAR.*
LOOKING TO 2020

November 10–11, 2020 | Leipzig, Germany
Leipzig Immune ONcology (LION) Conference
www.lion-conference.com
STRUCTURES AND FIGURES 2019
In light of an aging society and an increasing number of chronic diseases, modern medicine is facing exceptional challenges. The Fraunhofer Institute for Cell Therapy and Immunology IZI is working on meeting the demands of health and quality of life through new developments in the fields of diagnostics and therapy. Our body’s immune detection and defense system are of particular interest here, as well as cell-biological assay and treatment methods.

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 for the business units Cell and Gene Therapy, Drugs and Diagnostics. Its areas of competence lie in cell biology, immunology, drug biochemistry, bioanalytics and bioproduction as well as process development and automation. The research focus is on developments in the field of immunoncology and infection research.

The institute works in close cooperation with hospital institutions and performs quality tests besides carrying out the GMP-compliant manufacture of investigational medicinal products. Furthermore, it helps partners obtain manufacturing licenses and permits.
BUSINESS UNITS

CELL AND GENE THERAPY
- Drugs & target discovery
  - Biomarkers
  - OMICS-platforms (genome, RNA, proteome)
  - Bioinformatics
  - Cell analytics
- Therapy & diagnosis concept
  - In vitro studies
  - Bioanalytics
  - Pharmacology
  - Vaccines
  - Antibodies
  - ATMPs
  - Small molecules
- Preclinic & validation
  - In vivo studies
  - GLP testing
  - Toxicology

DRUGS & BIOLOGICALS
- Manufacturing
  - Process development
  - GLP testing
  - Toxicology
  - Manufacturing authorization
- Clinical trials
  - Quality management
  - Companion diagnostics
  - Manufacturing authorization

DIAGNOSTICS
- Approval
  - Regulatory expertise from preclinic through to approval
  - GMP manufacturing
COMPETENCIES AND INDICATIONS

- **Therapeutic Molecules**
  - allergies
  - infections
  - inflammation
  - autoimmune diseases
  - immunology
  - immune tolerance

- **Cell Techniques**
  - hematology
  - oncology
  - tumors
  - stroke

- **Bioanalytics**
  - neuropathology

- **Biomarkers**
  - protein misfolding diseases

- **Compilations and Indications**
  - immunology
  - hematology
  - oncology
ORGANIZATION LEIPZIG HEADQUARTERS

MAY 1, 2020

DIRECTOR
Prof. Dr. Ulrike Köhl

ADMINISTRATION
Anja Bochmann-Seidel | Annette Schäfer (deputy)

EXECUTIVE DEPARTMENTS

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

CENTRAL FACILITIES

— Center for Experimental Medicine
  Dr. Thomas Grunwald
— Imaging
  Prof. Dr. Ulf-Dietrich Braumann
— GLP Test Facility
  Dr. Jörg Lehmann

OFFICERS

DIRECTOR
Prof. Dr. Ulrike Köhl

MAIN DEPARTMENT
OF GMP CELL AND
GENE THERAPY
Dr. Gerno Schmiedeknecht | Kati Kebbel

DEPARTMENT OF
GMP PROCESS
DEVELOPMENT
PD Dr. Stephan Fricke

DEPARTMENT OF
THERAPY VALIDATION
Dr. Jörg Lehmann

DEPARTMENT OF
IMMUNOLOGY

— Preclinical Models,
  Sina Riemschneider
— Immunology,
  Prof. Dr. Stefan Kalkhof
— Cell Line Development,
  Dr. Elke Lieberman
— Manufacturing
  Biopharmaceuticals,
  Dr. Lukasz Budak
— Quality Control
  Biopharmaceuticals,
  Dr. Jens Knauer
— Veterinary Pathology,
  Dr. Anke Hoffmann

DEPARTMENT OF
CELL THERAPY

Dr. Thomas Grunwald | Dr. Stephan Klöß

— Experimental Imaging,
  Dr. Sebastian Greiser
— Clinic-oriented
  Therapy Assessment,
  Dr. Antje Dreyer
— Branch Lab
  Translational Cell
  Therapy (Hannover),
  Dr. Stephan Klöß

DEPARTMENT OF
DIAGNOSTICS

Prof. Dr. Friedemann Horn

— Inflammation Models
  and Immuno-
  diagnostics,
  Dr. Franziska Lange
— MicroDiagnoscs,
  Dr. Dirk Kuhlmeier
— DNA Nanodevices,
  Dr. David M. Smith
— CardiOomics,
  Prof. Dr. Dr. Dr.
  Andreas Oberbach
— Next-Generation
  Diagnostics,
  Dr. Conny Blumert
— Bioinformatics,
  Dr. Kristin Reiche

HEADQUARTER LEIPZIG
ORGANIZATION BRANCHES
MAY 1, 2020

BRANCH BIOANALYTICS AND BIOPROCESSES
Dr. Eva Ehrentreich-Förster (temp.)

MARKETING & COMMUNICATION
Dr. Katharina Kasack

ADMINISTRATION
Katja Okulla

DEPARTMENT OF BIOSYSTEMS INTEGRATION AND PROCESS AUTOMATION
PD Dr. Ralph Hölzel (temp.)

DEPARTMENT OF DRUG DESIGN AND TARGET VALIDATION
Molecular Biotechnology, Dr. Holger Cynis
Protein and Drug Biochemistry, PD Dr. Stephan Schilling
Drug Design and Analytical Chemistry, Dr. Mirko Buchholz
Protein Misfolding Diseases, Dr. Anja Schütze

DEPARTMENT OF MOLECULAR AND CELLULAR BIOANALYTICS
Dr. Eva Ehrentreich-Förster

DEPARTMENT OF CELL-FREE AND CELL-BASED BIOPRODUCTION
Dr. Stefan Kubick

ROSTOCK

HALLE (SAALE)

POTSDAM-GOLM
KEY INSTITUTE FIGURES 2019
AS AT DECEMBER 31, 2019

PROJECT REVENUE
by funding agency

50.6 % Industry
(TEUR 17,412)
26.6 % German national and regional government
(TEUR 9,166)
21.9 % Other (TEUR 7,520)
0.9 % EU (TEUR 304)

€ 34.4 MIO PROJECT REVENUE
by location in € mio

26.07

Leipzig
Potsdam-Golm
Halle (Saale)
Rostock

EMPLOYEES
Workforce composition

57 % Scientists incl. visiting scientists
15 % Technical assistants and laboratory technicians
10 % Administration / executive departments / IT and technical infrastructure
7 % Student / scientific assistants
6 % PhD students
5 % Interns / degree candidates / Bachelor students / Master students / trainees

661 EMPLOYEES
by location

443

Leipzig
Potsdam-Golm
Halle (Saale)
Rostock
RESEARCH INFRASTRUCTURE
AT THE LEIPZIG SITE

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

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

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

RENTAL AREA AT BIO CITY LEIPZIG
Start-up operations: 2006
Clean rooms: 334 m²
DEPARTMENTS
LOCATION LEIPZIG, GERMANY

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

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

**CORE COMPETENCIES**
- Quality assurance
- 1 000 m² clean rooms
- ATMPs
- Process transfer and development
- Manufacturing authorization according to §13 AMG
- Investigational Medicinal Drug Dossiers (IMPD)
- Good Manufacturing Practice (GMP)

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**PROJECT EXAMPLES**

**MANUFACTURE OF KYMRIAH®**

The CAR-T cell therapy is a new type of cancer immunotherapy that uses the patient’s own T cells to fight certain types of cancer. In order to do this, the cells are collected in the clinic by leukapheresis and then genetically reprogrammed in vitro in such a way that they can use a chimeric antigen receptor (CAR) to recognize cancer cells and other cells that have a special antigen on their surface. Following lymphodepleting chemotherapy, the reprogrammed cells are administered to the patient though an infusion. They then proliferate and can trigger the immune response.

In August 2017, the first CAR-T cell therapy became available in the USA in the form of Kymriah® (CTL019 / tisagenlecleucel). Kymriah® was granted FDA approval for children and young adults aged up to 25 years old diagnosed with acute lymphocytic B-cell leukemia (ALL) who are not responding to the usual therapies or have already suffered relapses. In May 2018, approval was also granted for adult patients with diffuse large B-cell lymphoma (DLBCL) who had suffered relapses after two or more lines of systemic therapy or who have not responded to therapy at all. On August 27, 2018, Novartis announced that it had received approval from the European Commission for both of these indications based on the recommendation given by the European Medicines Agency (EMA).

Fraunhofer IZI has long been an important manufacturing and development site for this innovative CAR-T cell therapy for clinical trials throughout Europe. Currently, prescription-only, approved T-cell therapies will also be manufactured on an interim basis in the Main Department of GMP Cell and Gene Therapy at Fraunhofer IZI, alongside investigational medicinal products. Following a one-year technology transfer period from Novartis’ Morris Plains site in New Jersey, USA, and after obtaining manufacturing authorization in accordance with Section 13 of the German Drug Act (AMG), the first clinical batch was manufactured at Fraunhofer IZI in Leipzig in August 2016. Since then, the Main Department of GMP Cell and Gene Therapy has continuously produced CAR-T cell therapies for Novartis.

Until the end of 2019, several 100 batches were delivered to patients, including many children, all across Europe. The extremely complex process involved in manufacturing a Kymriah®-Batch takes several days and involves not only state-of-the-art instrument engineering, but also manual tasks. Before being released for human use, extensive analytical release tests are first conducted on the finished product (e.g. concerning identity, purity, in vitro potency, microbiological safety) and the batch documentation is reviewed in detail.

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1. **Manufacture of Kymriah® in the clean room.**
2. **Quality of Kymriah® is examined in the quality control laboratory.**
ROR1 CAR-T POC INITIATIVE: CAR-T CELLS FOR THE TREATMENT OF BREAST AND LUNG CANCER

With the so-called CAR-T cell therapy, the US Food and Drug Administration (FDA) approved a gene therapy for the first time in 2017 which has already resulted in impressive treatment outcomes in clinical trials involving cancer patients. This revolutionary form of therapy is also the basis of the ROR1 CAR-T research project.

The chimeric antigen receptor (CAR) developed at the University Hospital of Würzburg recognizes the ROR1 molecule, which is expressed in cancer cells in leukemia, for example, as well as in breast and lung cancer. In order to manufacture the cell product, immune cells are first taken from the patient’s body by leukapheresis. T helper cells and cytotoxic T cells are then selected by magnetic cell separation. The genetic material for the CAR is introduced into the genome of the T cells via a non-viral gene transfer using the so-called “Sleeping Beauty” transposon system (jumping gene). This reprograms the T cells in such a way that they recognize ROR1-positive cancer cells as “foreign” and eliminate them by releasing cytotoxic messengers. The reprogrammed cells are expanded and administered to the patients intravenously.

The project is being funded as a pilot project under the proof-of-concept initiative launched by the Fraunhofer-Gesellschaft, the Helmholtz Association and Deutsche Hochschulmedizin in order to promote the translation of innovative research projects. The funding will support the conduct of preclinical trials into the safety and efficacy of the ROR1 CAR-T cells and drive clinical translation into a phase I / II study (first in human).

Based on the successful process development on a small scale, an initial test batch adjusted to reflect the actual production scale was manufactured as part of the project, which will be used to further optimize the process with an eye to the stringent production requirements under GMP conditions. At the same time, the required equipment was qualified, the suitability of newly introduced GMP-compliant materials checked and the respective specifications compiled in order to guarantee the consistent quality of these materials. After additional test batches have been completed, the manufacturing process is expected to be validated in the third quarter of 2020. The analytical methods that form part of the so-called safety parameters (mycoplasma, sterility, bacterial endotoxins, vector copy number) are planned to be validated at the same time. An application will be sent to the responsible authority, i.e. Landesdirektion Sachsen (Saxony Land authorities), simultaneously for the manufacturing permit pursuant to Section 13 of the German Drug Act.

1 Loading the tubing set for selection onto the CliniMACS Plus.
2 Preparing for transfection with the MaxCyte GTx.
3 Removing the cassette following completion of transfection.

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DEPARTMENT OF GMP PROCESS DEVELOPMENT
The GMP Process Development Unit 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.

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

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

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

PRECLINICAL DEVELOPMENT OF AN ADVANCED THERAPY MEDICINAL PRODUCT (ATMP, PALINTRA®) FOR THE PREVENTION OF GRAFT VersUS HOST DISEASE (GVHD)

The main complication that occurs following hematopoietic stem cell transplantation is graft-versus-host disease (GvHD). The immune response demonstrated by the transplant to the host can prove fatal or result in serious long-term damage and a lifelong need for treatment. Clinical symptoms include inflammation that usually affects the skin, intestine and liver. There is an over 30 percent chance that acute GvHD (grades II to IV) will emerge following stem cell transplantation; this figure rises to 40 percent for chronic GvHD. In terms of pathophysiology, GvHD is triggered by the donor’s immunocompetent T cells. These cells recognize antigens from the recipient, which leads to the activation, expansion and release of pro-inflammatory factors besides the activation of additional inflammatory cascades, causing tissue damage in the affected areas.

Current immunosuppression strategies for treating and/or preventing GvHD often prove inadequate, making it all the more necessary for new treatment options for GvHD to be developed as soon as possible.

The GMP Process Development Unit is working on protocols and procedures in preparation for manufacturing an ATMP (advanced therapy medicinal product) to help prevent GvHD under GMP conditions.

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LOCATION LEIPZIG, GERMANY

DEPARTMENT OF THERAPY VALIDATION
The department was founded in January 2016 as a direct replacement of the former Cell Engineering / GLP unit. The main goal of the new department is the concentration of expertise for the preclinical validation of novel therapeutic approaches at IZI, to maximize the efficiency in developing new in vitro or in vivo models and their application in preclinical studies. Since the department manages the GLP test facility of Fraunhofer IZI, all preclinical studies (even those in other IZI departments) can be performed under GLP.

THE DEPARTMENT COVERS THE FOLLOWING TOPICS

1) 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.

2) 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).

3) Identifying and validating new protein biomarkers for diagnosis and therapy of chronic-inflammatory and tumor diseases, as well as for the sector of veterinary medicine / farm animal husbandry.

4) Developing human therapeutic monoclonal antibodies for the treatment of tumor and autoimmune diseases, as well as for passive vaccination against bacterial toxins and pathogenic viruses, and their advancement to drug candidates.

5) GMP-compliant production of clinical test samples, e.g. recombinant proteins (manufacturing authorization pursuant to Section 13 of the AMG obtained on July 12, 2018), in a separate clean room facility.

CORE COMPETENCIES

- Preclinical studies
- Good laboratory practice
- Immunotoxicology (study design and implementation)
- Protein biomarker (identification and validation)
- Antibody and immunoassay development (diagnostics)

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UNITS

PRECLINICAL MODELS UNIT

The Preclinical Model Unit is concerned with the design and implementation of preclinical efficacy and safety studies for new drug candidates under GLP or GLP-analogous conditions. This includes the development, establishment and validation of in vitro and in vivo models for inflammatory and tumorigenic diseases. The main focus of research is on the development and optimization of humanized mouse models for developing and testing patient-specific therapies.

PROTEIN BIOMARKER UNIT

The Protein Biomarker Unit focuses on the identification and validation of proteins to be used as diagnostic biomarkers or representing therapeutic targets particularly in the context of developing and testing novel implants as well as for the medical indications triple-negative breast cancer and chronic inflammatory bowel disease. Multi-omics strategies (especially LC-MS based proteomics) are applied for biomarker detection as well as for the study of disease- or agent-induced effects.

Prof. Dr. Stefan Kalkhof also holds a research professorship position for instrumental bioanalytics at the Coburg University for Applied Science. This synergy enables the application of additional spectroscopic and mass spectrometric approaches e.g. for the direct chemical analysis of implants.

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ANTIBODY PRODUCTION UNIT

The Antibody Production Unit operates a state-of-the-art clean room facility for the GMP-compliant manufacturing of recombinant proteins based on, for example, CHO cell lines. The modular production facility covers clean room categories D to A and stands out due to its high level of flexibility achieved, amongst others, by using single-use disposables. The range of services includes the planning, development and implementation of manufacturing processes and quality control for preclinical and clinical test samples (up to phase II). Test samples can be produced either in bulk or in individual doses.

CELL LINE DEVELOPMENT UNIT

The Cell Line Development Unit is focused on the detection strategies of biomarkers and molecules based on monoclonal antibodies produced in house. Building on our experience in the field of human and veterinary diagnostics as well as in the area of food allergy analytics, we are working with the user to develop immunology singleplex and multiplex assays. Extraction for the purpose of restoring epitope accessibility in complex, denatured matrices represents a key topic and is especially relevant for the equivalent recovery of analytes in multiplex bead assays. With regard to cell line development for biopharmaceuticals, we draw not only on automated cloning and selection, but also on the label-free detection of biomolecules in real time by means of surface plasmon resonance spectroscopy (SPR). This enables the product to be quantified and characterized at early stages within cell line development, allowing the course for optimization planning to be set in good time.
VETERINARY PATHOLOGY UNIT

The Veterinary Pathology Unit carries out histopathological and toxicopathological examinations as part of GLP studies investigating the safety and efficacy of drug candidates. In accordance with the regulatory requirements concerning test candidates for new drugs or medical devices, tests for local effects after application and / or toxicity testing, for instance, are carried out in order to ensure that the test candidates are not expected to pose any health risks.

The unit's portfolio covers the planning, drafting, validation, implementation and evaluation of histological test procedures. All work processes, from sampling to processing through to the appropriate histochemical and IHC staining of tissue sections, are carried out in line with relevant SOPs. Various sample systems generated by the group such as paraffin-embedded and cryo-preserved tissue samples, stained tissue sections and also remaining samples are collected in a biobank and archived in compliance with GLP following study completion. The digitalization of tissue sections completes the GLP trial portfolio.

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CONDUCT OF GLP TOXICITY STUDIES TO APPLY FOR TEST CATEGORY 2

In 2009, the Department of Therapy Validation was recognized by the Saxon State Ministry of the Environment and Agriculture in Dresden as a test facility for conducting non-clinical drug trials under the quality assurance system of good laboratory practice (GLP) in test category 9. The test facility is therefore permitted to conduct non-clinical efficacy and safety studies involving various drug candidates such as advanced therapy medicinal products (ATMPs) and medical devices. The first GLP study to evaluate the migratory and tumorigenic behavior of a now commercially available autologous cell therapy for the treatment of articular cartilage defects was concluded in 2014. The safety and risk profile for the therapy’s potential use in humans was able to be assessed based on the results of this study, following the application of the cell therapy in the mouse model. This was then used to help justify a clinical trial involving human subjects. In 2020, the GLP test facility will be working on an application for test category 2, which would enable it to expand its safety testing portfolio. In test category 2, toxicological properties are recorded based on defined research parameters following the application of new drug candidates in a suitable animal model in order to assess possible toxic effects on humans. The study forming the basis of the application will evaluate the systemic toxicity of a therapeutic hepatitis B vaccine following repeated intramuscular application in the mouse model in accordance with the regulatory guidelines of the EMA (CPMP/SWP/465/95) and the WHO (WHO Technical Report Series, No. 927, 2005 Annex 1). The study is being funded under the proof-of-concept initiative together with Helmholtz Zentrum München (German Research Center for Environmental Health) and the Technical University of Munich (Rechts der Isar Hospital) as well as University Medical Center Hamburg-Eppendorf. The Veterinary Pathology working group will carry out the histopathological appraisal of the organs and tissues besides recording and evaluating the test results. The expansion into test category 2 will mark another significant strategic milestone for Fraunhofer IZI’s GLP test facility in terms of broadening its expertise and complementing existing safety testing for new drug candidates and medical devices.

1. Following their removal, organs and tissue taken from the mouse are processed before being examined and analyzed on microscope slides. Various tissue cassettes and a paraffin block can be seen next to the stained tissue sections.

2. Tissue sections 3–5 µm in thickness are prepared using the rotary microtome before being placed on microscope slides and stained.

PROJECT EXAMPLES

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DEVELOPMENT OF A NOVEL THERAPEUTIC CONCEPT FOR CHRONIC INFLAMMATORY BOWEL DISEASES (IBD) VIA NON-TOXIC LIGANDS OF THE ARYL HYDROCARBON RECEPTOR

The umbrella term chronic inflammatory bowel disease (IBD) covers disease patterns that are characterized by recurring or continuously emerging inflammatory changes to the bowels. The two main types of IBD are Crohn’s disease and ulcerative colitis. In Germany, around 300,000 people currently suffer from these two disorders, which are associated with long-term abdominal pain and diarrhea as well as high levels of fatigue.

Conventional IBD therapies focus on repressing the inflammation using anti-inflammatory drugs. A cure is yet to be found for these diseases, which means any drug therapy generally has to be administered for a person’s entire lifetime. This is first and foremost due to the fact that these therapies are systemic treatments. A therapeutic approach is yet to be found which has a causal and sustainable impact on the dysregulation of the intestinal immune system associated with IBD. Surgical measures often give rise to complications and impact on quality of life. The gut microbiome, which is significantly influenced not only by nutrition but also by the use of antibiotics, plays an important role in the emergence of IBD. This is why nutrition and alternatives to antibiotics are playing an increasing role in the development of new approaches to treating these diseases. More recent studies attest to the fact that the aryl hydrocarbon receptor (AhR) presents a highly promising, novel therapeutic target in the case of IBD.

Furthermore, numerous research papers have shown that the AhR plays a significant role in both the innate and the adaptive immune system in terms of maintaining immune homeostasis and controlling inflammatory responses in the intestines. The AhR is central to the communication between immune cells and enterocytes. AhR ligands found in food or the microbiota activate the AhR, promoting the survival and proliferation of immune cells and making a substantial contribution to immune homeostasis. Based on the recently published AhR structure, a highly diagnostic pharmacophore model is to be developed which will be used to select new, previously unknown AhR ligands as candidates for future therapeutic application in IBD cases using structure- and ligand-based methods. Moreover, a drug repositioning approach is to be taken, i.e. drugs which have already been approved or drug candidates currently undergoing clinical testing are to be identified as potential AhR ligands for other indications.

This work was supported by the Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD.

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Therapeutic effect of plant AhR ligands indole-3-carbinol (I3C) and quercetin (Q) in a mouse model of chronic dextran sulphate induced colitis, shown as an improvement of the cumulative clinical score.

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SYSTEMS MEDICINE APPROACH FOR PERSONALIZED BONE DEFECT TREATMENT IN PATIENTS COMORBID WITH TYPE-2 DIABETES (SYMBOD)

Bone possesses the remarkable feature of healing without forming a fibrous scar tissue. However, fracture healing may be compromised under certain disease conditions. Type-2 diabetes mellitus is a metabolic disease known to reduce the vascularization and innervations of regenerated tissue and thus may impair the healing capacities of bones. The central hypothesis of the SyMBoD projects is that the application of individualized and resorbable scaffold materials will guide bone tissue in regeneration and thus improve the fracture healing process. However, if and to which extent such a healing support is necessary depends on the patient’s individual traits and further comorbidities.

Yet, there is no diagnostic method to identify patients prone to compromised bone healing at beginning of the therapy. To this end, the SyMBoD projects aims to develop a digital platform for decision-making on individualized therapy plans for patients diagnosed with T2DM. This includes (i) the identification of theranostic biomarkers for early outcome prediction and therapy decision and (ii) the modeling of individualized, patient- and fracture-specific scaffolds for fracture bridging.

As one column of the platform comprehensive and time-resolved molecular patterns of animal studies and human biobank specimen will be collected using transcriptomics, proteomics and metabolomics. By applying bioinformatic approaches data can be correlated to observe healing processes leading to molecular models and theranostic biomarkers. This will guide the patient stratification and identification of risk groups.

As the second column of the platform scaffold materials for bone applications will be optimized by iterative testing in animals. Multi-scaling modeling will be applied for (i) optimizing biomechanical properties of scaffolds of different sizes and (ii) developing computer models to predict optimized individualized patient- and fracture-specific scaffolds.

Both, molecular and biomechanical models will be integrated into a systems medicine digital platform that will support clinicians with identifying patients prone to compromised bone healing and allow the seamless modelling of an optimized and individualized scaffold. Finally, real bone implants can be manufactured from these models in a GMP-compliant manner by applying CAD-CAM 3-D printing techniques with biocompatible and resorbable materials thereby breaking ground for the first individualized therapy in bone reconstruction.

PROJECT FUNDING

1 Critical size bone fractures are in the focus in the SyMBoD project. Photo © praisaeng - stock.adobe.com
2 Digital platform for individual fracture treatment in T2DM patients.
DEPARTMENT OF IMMUNOLOGY
THE DEPARTMENT AT A GLANCE

Procedures to stimulate or suppress the immune system are developed in the Department of Immunology. 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. A further topic is improving the problem-free healing of transplants by the induction of specific tolerance. Furthermore, procedures are being developed to monitor immunoreactivity and to control dysfunctions such as graft-versus-host disease (GvHD). Bacteriostatic peptides and peptide banks for the analysis of immune reactions in food allergies are a further focus. Novel imaging procedures help analyze immunological and cell biological processes.

CORE COMPETENCIES

- Antimicrobial peptides
- Immunome mapping
- Vaccine development
- Immunological models
- Tolerance induction
- Inactivation of pathogens / antibody development
VACCINE TECHNOLOGIES UNIT

The unit develops diagnostic techniques and prevention strategies for infectious diseases in human and veterinary medicine. The main research focus is on viral and bacterial infections affecting livestock and zoonotic diseases. Pathogens up to biosafety level 3 can also be processed. Marker vaccines are developed which enable differentiation between infected and vaccinated animals (DIVA strategy). All state-of-the-art methods in virology, microbiology, molecular biology and immunology are well established in the unit. Viruses currently being focussed on include West Nile Virus, dengue, Zika viruses or influenza. Besides this, strategies are being developed to combat ectoparasites. In addition, large-animal models can be provided through the collaboration with the Faculty of Veterinary Medicine at Leipzig University.

LIGAND DEVELOPMENT UNIT

This group applies statistical peptide phage display for the epitope mapping of antibodies (from sera, e.g. allergy and infectious disease diagnostics) as well as for the discovery of novel therapeutic or cell specific ligands. Another topic is in vitro tissue and organoid models for which cutting-edge equipment (FACS, imaging) as well as patented methods to generate iPS cells or surface modifications for cell cultivation are available. One successful spin-off and one more in preparation are testament to the rapid translation of applied research into commercial usage.
ANTIMICROBIAL AGENTS UNIT

The aim of this unit is to develop peptides which have an antimicrobial effect to fight multiresistant germs, such as *Staphylococcus aureus*, vancomycin-resistant enterococci, *Candida albicans*, etc., as well as their evaluation in respective animal models. The main focus here is on applications in the field of dentistry and oral hygiene. A further key focus is placed on identifying and evaluating plant compounds for applications in the fields of immunomodulation, inflammation inhibition, concomitant tumor therapy and antibiosis.

 IMMUNE TOLERANCE UNIT

The goal of this unit is to develop cell- and antibody-based therapeutic strategies to treat complications following hematopoietic stem cell transplantation. Novel concepts of immunological tolerance which take into account immunological and therapy-associated complications (e.g. GvHD) are being tested in new, in-house developed models. The structure of the GMP Process Development Unit guarantees a direct translation of novel therapeutic approaches for ATMPs.

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PRECLINICAL VALIDATION UNIT

This unit develops and examines new vaccines and drugs in preclinical trials. Drugs and vaccine candidates are tested in vitro in cell culture systems and in vivo in preclinical trials involving different animal species, also under GLP conditions. This research is focused in part on the development and efficacy testing of innovative vaccines for humans and animals.

IMAGE ANALYSIS OF CELL FUNCTION UNIT

This unit develops new methods for the non-destructive, microscopy-based quantification of physiological and pathological processes. The aim is to support research into fundamental biological connections and to test new therapy procedures by analyzing cells and tissue without their modification or destruction. As this objective requires interdisciplinary cooperation in the fields of electrical engineering, optics, imaging, software development and biology, the specialist group has close ties to the Chair for Biotronic Systems, Faculty of Engineering at Leipzig University of Applied Sciences (HTWK Leipzig).

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BIOLOGICAL MATERIAL ANALYTICS UNIT

The Fraunhofer IKTS working group is based at Fraunhofer IZI and primarily focuses on developing standardized biocompatibility and immunocompatibility tests for assessing implant materials. This includes developing models based on immune cells and devising ways of standardizing the applied tests. Differentiation processes are combined with immunological tests here. This preclinical in vitro data enables conclusions to be drawn on the functionality of new materials depending on the patient’s immune system.

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INACTIVATION OF VIRUSES AND BACTERIA BY MEANS OF LOW-ENERGY ELECTRON IRRADIATION

The inactivation of pathogens using low-energy electron irradiation (LEEI) has long since been a key research area at Fraunhofer IZI. The ionizing radiation destroys the germs’ nucleic acids while leaving structural components such as proteins largely intact. This presents a significant advantage over chemical or other physical inactivation methods such as incubation with formaldehyde or heat treatment. Ionizing radiation techniques currently used for sterilization purposes (gamma or roentgen radiation) may only be utilized in specifically shielded buildings so as to avoid any danger being posed to people or the environment. This has prevented their use not only in normal biological and medical laboratories but also in biopharmaceutical manufacturing.

In close cooperation with the Fraunhofer Institutes IPA and FEP, an LEEI pilot facility has been developed that dispenses with major shielding structures. In the reporting year, various automated processes were established using the pilot facility which are able to fully inactivate pathogen suspensions on a multi-liter scale. This facilitates the use of the LEEI procedure in the production of pharmaceuticals. Several bacteria and viruses have been inactivated with the automated LEEI processes and investigations have been conducted into the preservation of the protein antigens following irradiation. The material was subsequently used in several vaccine studies. Taking respiratory syncytial virus (RSV) as an example, it could be shown that proteins, which play a decisive role in inducing a protective immune response, are hardly damaged as a result of irradiation. A complete protective effect could therefore be offered by the vaccine based on the material. These experiments form the basis of the further development of LEEI-based pharmaceutical drugs. In collaboration with a leading company from the field of laboratory automation, devices are now being developed that facilitate the integration of LEEI in industrial manufacturing processes.
DEVELOPMENT OF BIODEGRADABLE PESTICIDES BASED ON PLANT EXTRACTS WITH AN ANTIMICROBIAL EFFECT

Plant-damaging fungi are increasingly becoming a problem for the global food supply both in western industrialized nations and in developing countries. At the same time, it has become clear in recent years that the antifungal treatment strategies currently in place for plants and fruit are often inadequate as harmful fungi are increasingly developing resistances. This happens in particular when fungicides are unable to be used in a sufficient dose so as to comply with set limit values in crops. The demand for ecologically compatible fungicides with low off-target toxicity is therefore of huge interest.

The need for innovative, plant-based alternatives to fungicides (referred to as botanicals) is also clear from the fact that many current fungicides have to be withdrawn from the market after just a few years due to their side effects. Besides this, EU Directive 1107/2009 states that botanical and extract-based plant protection products are to be approved ahead of synthetically manufactured products based on single substances. Botanicals-based fungicides offer a number of advantages, e.g. they are biodegradable, can be used in organic farming and they do not accumulate in food / along the food chain. Furthermore, plant extracts usually comprise several constituents acting independently of each other. This makes it more difficult for phytopathogenic fungi to develop resistances to the fungicidal constituents of these plant extracts.

The harmful fungi in question, for which a control strategy is to be developed based on plant extracts, generally belong to the aspergillus, fusarium, botrytis, alternaria and penicillium species. Due to their high phytopathological potential and extremely harmful toxins, these fungi present not only an enormous risk to food production around the globe, their mycotoxins can also cause serious illnesses (e.g. tumor diseases, allergies).

In 2019, the Antimicrobial Agents Unit tested more than 30 plant extracts on relevant fungal species such as Fusarium graminearum, Botrytis cinerea and Penicillium expansum. As a result of this testing, four extracts were found to fully inhibit fungal growth both in vitro and in planta on corn and apples, at very low effective concentrations. These plant extracts could therefore provide an alternative to the antifungal plant protection products used to date. The four extracts will now undergo further analyses to investigate parameters relevant to approval such as their UV stability and rainfastness.

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1. Testing the effectiveness of the plant extracts against the harmful fungus Botrytis cinerea on apples.
2. Testing the effectiveness of the plant extracts against the harmful fungus Fusarium graminearum on wheat seeds.
PREVENTION OF ADVERSE IMMUNOLOGICAL COMPLICATIONS WHILE RETAINING THE ANTI-TUMOR EFFECT FOLLOWING STEM CELL TRANSPLANTATION USING ANTI-HUMAN CD4 ANTIBODIES

The main complication following an allogeneic hematopoietic stem cell transplantation is acute graft-versus-host-disease (aGvHD). The conventional treatment methods are frequently associated with low long-term success and toxicities. This necessitates the development of treatment alternatives which are less burdensome.

A new approach involves the use of a specific anti-human CD4 antibody. The antibody specifically reduces adverse immune reactions, thus minimizing the chances of aGvHD emerging following stem cell transplantation. The influence of this anti-human CD4 antibody with regard to the prevention of GvHD and under consideration of the graft-versus-leukemia (GvL) effect in a clinically relevant, humanized leukemia model is currently being investigated.

For this purpose models are being used which are particularly well suited for the transplantation of human hematopoietic stem cells and human leukemia cells. The findings are essential in applying the antibody and other new drugs in a hospital environment. Existing leukemia models are being further developed and the anti-human CD4 antibody and other drugs are being evaluated.

By using humanized models it may be possible to achieve new findings concerning immunological processes in the emergence of GvHD and regarding the GvL effect. The models and findings are not only extremely valuable for hematopoietic stem cell transplantation and leukemia treatment, but also for stem cell transplantation in other indications (e.g. autoimmune diseases).

1 Lung tissue, magnification x10 (HE).
2 Blood smear, magnification x100 (Pappenheim).
IMMUNOME MAPPING FOR PEPTIDE-IMMUNODIAGNOSTICS

Immunodiagnostic methods for diseases are usually based on proteins or extracts directly obtained from the pathogenic organism or produced with biotechnological methods. The disadvantage of this approach is that variants are difficult to distinguish, as commonly observed for influenza viruses. Protocols have been established to exactly identify the antibody binding sites (epitopes) of patient antibodies, which are also applicable directly to sera. This allows reliable identification of the pathogen, the causative antigen of allergies, or other indications like (auto)immune or infectious diseases as well as novel approaches for therapy and research.

A steadily growing number of allergy patients could be observed in recent years. Cross reactivities between food allergens reduce the significance of common allergy tests. Epitope-based diagnostics are probably the only alternative to clinical investigations, which require collection of venous blood. Only the provocation with the food is regarded as proof of an allergy, which has to be carried out under medical supervision in a clinic. An efficient diagnosis, appropriate treatment and dietary adjustments are therefore not available for many patients.

The Ligand Development Unit has been conducting research into the epitopes of allergenic soy proteins since 2013, covering an entire spectrum of validated peptide epitopes from allergenic food.

A particularly large project was funded by the Fraunhofer Zukunftsstiftung, which was followed nationally and internationally by allergologists with great interest. In cooperation with several other Fraunhofer institutes and hospitals, the FoodAllergen project aimed at dealing with food allergies using a holistic approach. This also includes the identification of allergens in foods and new processes of producing food ingredients with reduced allergenic potential. By the end of 2019, the epitopes for 14 plant allergens have been identified and many of them have already been tested/validated with more than 200 sera of the Fraunhofer IZI Allergy Biobank. Preparations for a spin-off of the project are already at an advanced stage.

Meanwhile, a new ERAnet project (POC4Allergy) started to develop alternative Point of Care (POC) test systems. The detection technologies are contributed by partners in France and Romania, the Charité in Berlin is once more the clinical partner.

1 Soybeans. Photo © S.Piyaset – Fotolia.
EFFICACY OF NOVEL HELICASE-PRIMASE-BASED THERAPY FOR HUMAN HERPES SIMPLEX VIRUS (HSV)

Currently, human Herpes Simplex Virus (HSV) infection affects about 82 percent 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 helicaseprimase inhibitors (HPIs), which use a novel mechanism of action to inhibit viral replication. The antiviral efficacy of new drug candidates for the treatment of HSV infections was analyzed in a drug development trial in a mouse model.

Despite the lower dose, we observed a better outcome in clinical parameters using HPI therapy in comparison to Valacyclovir control. No toxic side effects could be observed during the monitoring period of three weeks post infection. The subsequent analysis showed that treated animals harbor a significantly lower viral load compared with placebo animals.

In this project we showed that treatment with the new HPI candidates can significantly reduce or prevent clinical symptoms. HPIs 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.

1 Dose-dependent reduction of the amount of HSV-infected Vero cells (stained in red) treated with HPI.
VACCINATION AGAINST ASTHMA – MUCORSV

Approximately 235 million people worldwide suffer from asthma. Among children, asthma is the most widespread chronic disease, resulting in a severe impact on their quality of life. It has been shown that children who were infected with respiratory syncytial virus (RSV) in infancy or early childhood are more likely to develop asthma later. Glucocorticoids and beta-2 sympathomimetics are used as the standard therapy for asthma, but this treatment is often not sufficient in severe cases and can lead to significant side effects when used for long periods of time. An alternative treatment is therefore urgently required.

Due to the correlation between repeated RSV infections in early childhood and the development of asthma, preventive measures present the most effective mode of action. The MucoRSV project investigates whether a vaccination against RSV can protect from repeated infections and thus prevent asthma.

Currently there are no approved vaccines against RSV. Within the scope of this project, different vaccines will be tested and administered mucosally, i.e. via nasal spray or inhalation. One candidate is a killed vaccine containing virus particles which were inactivated by low-energy electron irradiation. The virus will be packaged in nanoparticles in order to enable an increased uptake via the mucosal membranes. Another vaccine consists of DNA coding for RSV-F, the most important RSV antigen. This DNA is packaged in non-human papilloma-virus capsids and applied using these viral vectors.

A vaccine against RSV could thus not only prevent the viral disease itself, but also reduce serious chronic consequences such as asthma.
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.
**RSV PROTECT**

While mostly harmless in healthy adults, Respiratory Syncytial Virus (RSV) is a severe risk to the lives of infants, the elderly, or patients with weakened immune systems. Additionally, RSV disproportionately impacts heavily populated, developing countries such as India or China, and is an increasing risk globally, causing an estimated number of more than 200,000 infant deaths yearly. While risk factors such as pollution or immune deficiency are known, true therapeutic and preventative measures are nearly non-existent. No RSV vaccine has cleared clinical trials despite 5 decades of failed efforts, and the only prophylactic on the market – Palivizumab (Synagis®) – is an expensive monoclonal antibody that is only used in the most high-risk patients in wealthy countries.

The RSV Protect team (Dr. Thomas Grunwald, Dr. Mirko Buchholz, Dr. David M Smith) has been working since 2016 to develop small molecules and synthetic biologics as effective, inexpensive lead compounds to inhibit the virus’s ability to enter and infect host cells. By creating compounds that bind to the receptors on the surface of the virus that are responsible for adhering to and fusing with host cells in lungs, the overall infectivity of the virus can be eliminated.

Using this strategy, several small peptides shorter than 15 amino acids were produced, which were targeted to “lock” the main fusion protein of the virus, RSV-F, in a configuration that leaves it unable to inject its genetic material into the host cells. These peptides, which are more than 100 times smaller than a typical antibody, were effective in micromolar concentrations at preventing RSV infections in both cellular model systems and living animals. Replacing essential amino acids in the sequence with non-natural, synthetic derivatives ensures their usability, increases their efficacy, and reduces the risk of unwanted side-effects.

Similar to most viruses, the numerous surface receptors on RSV work together as a deadly team, where 3 identical protein units are geometrically arranged in trimeric form to cooperatively enhance fusion with host cells. Therefore, the principle of multivalence was utilized to arrange 3 of the RSV-blocking peptides on a small structural scaffold made from DNA strands, geometrically complementary to the virus proteins. Presentation on this trivalent, DNA-peptide conjugate was successful in enhancing the protective ability of the peptides 500-fold in cell models, equivalent to levels seen for the only commercially available prophylactic, Palivizumab. This work has paved the way for a patent application and a broader, currently ongoing pre-clinical study.

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1 **RSV-F** protein enables the binding of the virus to the host cell and fusion with its plasma membrane, therefore infecting the cell. Molecular inhibitors developed in the RSV-Protect project lock RSV-F in its inactive configuration, preventing the virus infection of host cells.
LOCATIONS LEIPZIG AND HANNOVER, GERMANY

DEPARTMENT OF CELL THERAPY
THE DEPARTMENT AT A GLANCE

The Department of Cell Therapy prepares new gene and cell therapy procedures for clinical application. This involves the validation of experimental approaches with an eye to safety, feasibility and efficiency. Numerous model systems that facilitate the preclinical testing of novel concepts under the strictest quality criteria have been and continue to be established by the department. These systems lend the obtained results a high level of predictive power with regard to their future clinical application. Cell therapeutic methods are used, for instance, in the case of ischemic diseases such as stroke and myocardial infarction while attention is also given to processes that could prevent cell degeneration and aging. The “sleeping” potential of stem cells is also investigated. Last but not least, the department focuses on cell therapy methods in the field of immuno-oncology, where genetically modified immune cells (cytotoxic T-cells) or natural killer cells (NK cells) are developed to treat tumors.

CORE COMPETENCIES

- Experimental imaging
- Stroke models
- Cell therapeutics
- Preclinical study design
- Experimental neurosurgery
- Histology
- Gene modification of effector cells

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UNITS

EXPERIMENTAL IMAGING UNIT

Experimental imaging stands at the interface between engineering and life sciences. It is dedicated to research activities where the acquisition and processing of images are required before implementation is possible. This draws on different technical devices and software. As the methods used in the applied procedures are constantly being developed, the field of work is always adjusting to reflect the latest developments. The focus here lies on applying state-of-the-art imaging techniques as part of the task assigned to us by our respective project partners.

CLINIC-ORIENTED THERAPY ASSESSMENT UNIT

The unit tests and develops innovative diagnosis and therapy procedures for ischemic stroke. As the possibility of being able to transfer findings from current laboratory rodent models to human patients is sometimes only very limited, a globally unique large-animal model was established for the translational approach. Tests can be carried out using this model under clinically relevant and patient relevant conditions. Both the gyrencephalic brain structure and the size of the brain much more closely resemble the human situation in the sheep model as opposed to in the small animal.

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BRANCH LAB TRANSLATIONAL CELL THERAPY (HANNOVER)

The Branch Lab Translational Cell Therapy develops and validates cell-based advanced therapy medicinal products (ATMPs). To do this, it conducts translational research and develops GMP-compliant manufacturing protocols for cell therapeutics at the interface to preclinical development right through to their transfer into clinical trials. Cell and genetic engineering methods and strategies are implemented and optimized here to specifically manufacture killer lymphocytes and their subpopulations. The ability to overcome so-called tumor immune escape mechanisms in cancer cells is key here. This is achieved by using activated and genetically modified effector cells together with checkpoint inhibitors and stimulating immune cells. These cell therapies boost immune surveillance and strengthen the elimination of resistant cancer cells as well as their malignant precursor cells (so-called tumor stem cells). Another focus of development lies in optimizing the transduction capacity of effector cells using chimeric antigen receptors (CARs) in order to increase cytotoxicity to malignant cells. To do this, human effector cells are separated following lymphapheresis by means of GMP-suitable, fully automated, closed-system production, genetically modified as necessary and expanded as part of clinical upscaling. Moreover, the group is developing GMP-compliant manufacturing and expansion protocols in order to proliferate a sufficient number of activated effector cells.

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PROJECT EXAMPLES

COMBINATION OF DIRECTED, DUAL-SPECIFIC NK CELLS AND CHECKPOINT INHIBITORS FOR A HEIGHTENED EFFECT AGAINST RESISTANT HEAD AND NECK TUMORS AND TUMOR STEM CELLS

In this project, donor NK cells combined with specific receptors expressed on the cell surface referred to as chimeric antigen receptors (CARs) are manufactured with defined recognition molecules (CD133, CD44v6, HER1, HER2) to specifically target various surface structures / molecules on solid tumors, i.e. squamous cell carcinoma. As part of subsequent (in vitro) efficacy studies, specific recognition and elimination reactions of the activated CAR-NK cells are to be demonstrated against resistant CD133, CD44v6, HER1 or HER2-positive, malignant squamous cell carcinoma cells (cell lines and patient tumor cells). Further efficacy studies are then planned in humanized mouse tumor models (in vivo) using these genetically modified effector lymphocytes to demonstrate proof-of-principle and / or proof-of-concept for the cancer studies. Using this data, a directed, cell-based anti-cancer therapy is to be developed under GMP (good manufacturing practice) conditions, which will facilitate the successful, clinical treatment of patients in the future.

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PROOF OF PRINCIPLE FOR A FIRST IN CLASS NEUROPROTECTIVE THERAPY IN STROKE (SAVEBRAIN)

Stroke is the third leading cause of death beside cardiovascular and tumor disease and the main cause for disability in elderly people. Ischemic stroke is characterized by a cerebral hypoperfusion. This leads to a very low level of oxygen and nutrients of the neuronal tissue and therefore to neuronal damage and early loss of brain areas (primary damage). Due to the cell loss inflammation and apoptosis are initiated leading to secondary damage and a significant higher tissue loss even days after the ischemic event. As a consequence neurotoxic conditions are dominant in the brain. Therapeutic options are limited to recanalisation with recombinant plasminogen activator (rt-PA) having a very close therapeutic time window.

In this project a new therapeutic treatment is being evaluated targeting the inhibition of two neurotoxic mechanisms in comparison with activating a neuroprotecting pathway by combining three different substances. These agents affect the same cellular pathway. Their combination should enhance the clinical outcome through complete restoration of physiological conditions in the brain including the minimization of blood brain barrier breakdown as well as a decrease of tissue loss. One substance alone cannot achieve this and had to highly dosed probably occurring side effects. The three mechanisms of actions have already been validated in rodent studies. STAIR recommends testing in two different animal models with one model being gyrencephalic. This project used a stroke model in sheep. One hour after recanalisation of the middle cerebral artery animals received the three substances followed by imaging and behavioral testing over 28 days. A macrosopic and histological analysis of the brain tissue is performed at the end and compared to a control group.

PROJECT FUNDING

This project has received funding from the European Research Council (ERC) under the European Union’s Horizon 2020 research and innovation programme (grant agreement No 737586).

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1  MR imaging (DWI) of an acute stroke with the occlusion of the middle cerebral artery.
2  Illustration of a brain slice stained with TTV, red staining vital tissue, white areas necrotic brain regions (treatment group).
DEPARTMENT OF DIAGNOSTICS
DEPARTMENTS
DIAGNOSTICS

Fraunhofer IZI Annual Report 2019

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 was implemented for these processes and certification according to the ISO 9001 standard is planned for 2020.

A main focus of the department is the development of molecular diagnostic tests in the medical and food sector. This includes PCR and NGS analyses as well as lab-on-a-chip systems. Diagnostic needs are addressed for e.g. cancer, neurogenerative and inflammatory diseases as well as pathogen tests for infectious diseases. Currently, particular focus is being placed on diagnostic and prognostic tests for prostate carcinoma and the detection of pathogens in the field of cardiosurgery and sexually transmitted infections.

Beyond the molecular diagnostic field, the department has a wide range of additional analytical methods at its disposal and develops novel biointeractive molecules on structural DNA-based scaffolds. Furthermore, a large number of cell and animal experimental models are available. Xenogenic transplantation models are also used to bridge the gap between in vivo model and patient.

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THE DEPARTMENT AT A GLANCE

CORE COMPETENCIES
- Transcriptome analyses
- Next-generation-diagnostics
- Bioinformatics
- Nanotechnology
- Lab-on-chip
- Biomarker identification
- Tumor models
- Quality assurance according to DIN EN ISO9001
UNITS

INFLAMMATION MODELS AND IMMUNO_DIAGNOSTICS UNIT

This unit holds a broad spectrum of in vivo models for preclinical proof-of-concept studies. We focus on autoimmune induced joint diseases (e.g. Rheumatoid Arthritis), airway diseases (e.g. bronchial asthma, allergic rhinitis) and chronic kidney diseases. Other main topics are tumor models and humanized in vivo models. In addition, the group specializes in routinely developing new research models as well as in diverse methods of analysis to investigate the in vivo models.

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NEXT-GENERATION DIAGNOSTICS UNIT

This unit develops and establishes analysis strategies for discovering novel biomarkers to diagnose and anticipate diseases. The focus here is placed on the detection and characterization of RNAs, especially of non-protein-coding RNAs (ncRNAs), which possess a great deal of potential in terms of their use as biomarkers. The latest nucleic acid analysis techniques are employed here based on next-generation sequencing and microarrays. These procedures are being optimized to analyze various base materials (cryo tissue, FFPE tissue, urine, blood).

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DNA NANODEVICES UNIT

This unit focuses on exploring and developing DNA-based tools for biomedical research. In doing this, DNA molecules and their characteristics are used to arrange and structure biomaterials on the nanometer scale. This type of technology is applied to develop biosensors and nanocircuitry for biochips, in addition to being used to develop new procedures to specifically transport molecules in vivo and in vitro. To this end, the unit investigates the biochemical and biophysical characteristics of specific DNA molecules and composite materials in order to deduce concrete applications.

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MICRODIAGNOSTICS UNIT

The unit develops molecular diagnostic test systems for the food and medical-clinical area. A major focus is on the use of extracellular vesicles for the early diagnosis of Alzheimer’s or cancer, the development of rapid tests for infectious agents and bioanalytical sample preparation. Novel lab-on-a-chip diagnostic platforms, e.g. for the detection of sexually transmitted pathogens in home test format, are being developed with customers. Another focus is on airway analysis using ion mobility spectrometry. Hot embossing technology is available in-house for microfluidics development.

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BIOINFORMATICS UNIT

The Bioinformatics Unit develops and establishes computer aided ways of identifying and verifying new biomarkers for the personalized diagnosis and prognosis of diseases and for the detection of novel therapeutic targets. The fact that a vast number of RNA molecules are not translated into proteins has only been known for a few years. The latest scientific findings show that these non-coding RNAs (ncRNAs) perform fine regulatory tasks in gene regulation and are therefore suitable as markers for individual disease patterns and progression. The unit develops strategies for efficient processing and (statistical) analyzing molecular biological data gained from extensive clinical cohorts based on next-generation sequencing, microarrays, and DNA, RNA, and epigenetic analytics in order to detect disease-relevant ncRNAs. The gene regulatory mechanisms of ncRNAs are modeled using methods from systems biology and RNA bioinformatics. The objective of the unit is to analyze the potential of these innovative RNA molecules as biomarkers or therapeutic targets and to establish them as appropriate clinical markers or targets.

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CARDIOMICS UNIT

The group uses state-of-the-art OMICS technology platforms to research cardio-surgical locally and systemically relevant infectious diseases. The focus of scientific interest is in particular the crystallization of pathogen-specific virulence factors and their influence on the clinical outcome after implantation of a medically necessary device or implantation of biological or mechanical heart valves as well as their translation into clinical routine. Based on improved diagnostics, alternative treatment methods are evaluated and new interventional procedures taken to clinical maturity. In particular, the working group examines the relationship between infectious diseases and molecular regulatory mechanisms. In the interdisciplinary field of intervention strategies relating to cardiac surgery, the diagnosis and therapeutic intervention of the coagulation system play a vital role. The research group primarily develops diagnostic procedures for determining the effect of factor X inhibitors or coagulation diagnostics in the final section of the plasmatic and thrombocyti coagulation cascade.

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CAR-NK-CELL THERAPY FOR THE TREATMENT OF PERITONEAL METASTASES

Ovarian cancer is a highly aggressive cancer with a mortality rate of 70 percent. Due to the unspecific and late occurring symptoms, an early detection is often difficult. At this time point, the disease has often already affected the whole peritoneum with multiple metastases on many organs. The currently existing therapy is based on a radical surgical removal of the tumors as far as it is possible followed by a combined chemotherapy using paclitaxel and carboplatin. However, 20 percent of the cases have a primary platin resistance, so that a recurrence of the disease can be observed after 16–22 months. By the event of disease relapse, an immediate change of the therapy as well as alternative treatment strategies are decisive for the survival of the patients. Due to the fact that (i) surgical removal is more than difficult, (ii) radiation therapy is nearly impossible and (iii) chemotherapy is often ineffective, there is an urgent need for new therapeutic strategies treating this type of cancer.

NK-cell therapeutics carrying CARs (chimeric antigen receptors) are upcoming therapeutic approaches in the treatment of cancer because of their high efficacy and specificity and minor side effects compared to CAR T-cell therapies.

In this project, innovative NK-cell therapeutics with different CARs will be tested in a previously established orthotopic mouse model for peritoneal metastases. The metastases are induced by intraperitoneal injection of a luciferase labelled ovarian cancer cell line in highly immunodeficient NSG mice. After tumor cell transplantation, the mice are analyzed by different non-invasive imaging techniques particularly by Bioluminescence Imaging (BLI) to monitor tumor growth. Other imaging techniques such as CT or MRI are also possible, all devices are available at the Fraunhofer IZI animal facility. When the tumor load reaches a critical size, the treatment with CAR-NK cells begins. The therapeutic cells are also injected intraperitoneally. During the treatment period and in addition mice are monitored continuously by BLI to analyze the treatment effect. Finally, a model for ovarian cancer peritoneal metastases will be available which will allow testing cell therapeutics on a routine basis to develop innovative therapeutic strategies for the treatment of ovarian cancer.

Prospective projects could include a human immune system in the tumor mouse model for testing e.g. immune checkpoint inhibitors which need the interaction of immune cells for their mechanism of action.

![Peritoneal metastases (red arrows) in an NSG mouse 80 days after transplantation.](image1)

![SK-OV-3 cells used for this model.](image2)

**PROJECT EXAMPLES**

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1 Peritoneal metastases (red arrows) in an NSG mouse 80 days after transplantation.
2 SK-OV-3 cells used for this model.

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DIAGNOSTICS OF VARIOUS DISEASES IN EXHALED AIR USING ION MOBILITY SPECTROMETRY

The diagnosis of diseases should be as quick, easy and inexpensive as possible, directly at the point of care without highly qualified laboratory personnel and also without additional stress for the patient. To meet the existing requirements, research is being carried out at the Fraunhofer IZI and the Fraunhofer Project Center MEOS on a diagnostic method using exhaled air.

Breathing gas analysis has been used clinically for years as part of lung function tests or the urea breath test to detect Helicobacter pylori infections. However, there is a much greater potential in breathing gas diagnostics. There are thousands of so-called volatile organic compounds (VOCs) whose composition in the air we breathe changes with certain diseases and infections. For example, the diabetic patients’ smell of overripe fruit is known, caused by a greatly increased concentration of acetone, a VOC.

Most VOCs occur in extremely low concentrations (ppmV to pptV - one particle per million or trillion particles). This places extreme demands on the measurement technology. Conventionally, mass spectroscopic methods are mostly used, which, however, mean an enormously high expenditure on equipment. We therefore focus on ion mobility spectrometry (IMS), which is coupled with gas chromatographic (GC) pre-separation. This technology is much cheaper, more portable (shoebox size) and is already being used for drug and explosives controls.

In Leipzig, GC-IMS was able to differentiate between different bacteria based on their VOC profile after only 90 minutes of cultivation in the laboratory in 2019. In the course of the project, these experiences will now be used to directly examine real breath samples in the clinic. The aim is to diagnose various bacterial and viral infectious diseases, including any existing drug resistance, in patients’ breath.

In the MEOS project center in Erfurt, colleagues from Fraunhofer IZI and Fraunhofer IPMS are working on a new IMS system. The centerpiece is a small IMS silicon chip, which is being further developed at Fraunhofer IPMS in Dresden. Potentially miniaturized IMS chips can be inexpensively manufactured in large quantities using the microelectronic manufacturing processes. The new system is to be tested in the diagnosis of neurological diseases and cancer. In addition to the exhaled air, other non-invasive samples such as sweat and urine are also in focus.

GLYCO3DISPLAY – DNA-DIRECTED ASSEMBLY OF GLYCANS FOR ANTI-PATHOGEN SCREENING

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. This approach leads to precise arrangements of defined glycan chains being created with single-nanometer spatial resolution. This brings together two key technologies from partners Fraunhofer IZI and the Max Planck Institute for Colloids and Interfaces: DNA Nanotechnology and Automated Glycan Synthesis.

In the early phases of the project, work focused on creating a high-throughput assay for investigating the binding of specific glycan formulations and arrangements to target pathogens like E. coli bacteria. 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.

Using the information gained from this assay system, new DNA-glycan compounds can be designed for both diagnostic and therapeutic purposes. By covering the surface of viruses or bacteria with these compounds, their ability to infect host cells can be significantly hindered. These types of “anti-adhesive” or “fusion inhibition” compounds are increasingly being developed for medical markets. Similarly, the specific binding of these DNA-glycan compounds to the surface of pathogens can be utilized instead of traditional capture antibodies in advanced disease diagnostics.

1 Sugar molecules are conjugated to small, branched DNA structures formed from 4 individual DNA strands. When bound to magnetic beads, these can be used for the high-throughput screening of how compounds bind to bacteria like E. coli.
THE DEPARTMENT AT A GLANCE

The department focuses on the development and evaluation of extracorporeal (outside the body), organsupporting technologies with a particular emphasis on supporting the immune system. We offer 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, we offer 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

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PROJECT EXAMPLES

EX SITU ORGAN PERFUSION

The availability of suitable donor organs for patients with organ failure has been a major problem for many years. On the one hand, the number of donations itself is too low – it is estimated that only about ten percent of the actual demand can be met with transplanted organs. On the other hand, the functionality of donated organs or the health status of potential donors often does not meet medical requirements. Pre-existing diseases of the donor, the presence of risk parameters, especially in the case of livers, e.g. a high degree of adiposity, but also the duration of the ischemic period (lack of blood and oxygen supply to the organ during transport) after organ removal can lead to considerable organ functional losses. Such “marginal” organs usually mean a lower probability of survival for the transplanted patient, or are not even considered as donor organs. However, due to the high demand for donated organs, there is a growing desire to also consider marginal organs for transplantation.

This is where the "OrganFit" project comes in. It is already known from published work that organs can be kept functional for a certain period of time by means of machine perfusion. If the perfusion is then carried out at physiological temperatures (“normothermic”), the preservation of function is improved compared to hypothermic conditions, as the cold ischemia time is reduced.

The organ perfusion platform established in the EXIM department in Rostock will now be used to investigate further approaches that will support the use of marginal livers. For this purpose, both technical and biological approaches are planned to support or even strengthen the natural regeneration potential of livers. Livers from pigs will initially be used to establish and test these approaches. The project is carried out in close cooperation with the Clinic for Transplantation Surgery and the Clinic for Anaesthesia and Intensive Care Medicine of the University Medicine Rostock.

Looking beyond the current project, the technical platform should also enable new cooperations and further research projects and thus make the most diverse use of the opportunities offered by ex situ organ perfusion.

1  Technical set-up of the perfusion platform.
2  Preparation of a pig liver for perfusion.
CRYOREGENERATION OF DIALYSATE

Patients whose bodies have a weakened detoxification function due to a late-stage chronic kidney disease regularly need to have dialysis. The principle behind this procedure has been established for decades and is based on extracting water-soluble toxins (uremia toxins) in an extracorporeal filter, i.e. the dialyzer. The toxins pass from the blood into the purifying dialysis water (dialysate) via a membrane in the dialyzer. Around 120 liters of dialysate are required for every dialysis treatment, which usually takes four hours and is repeated three times a week. This water is taken from reverse osmosis (RO) plants in hospitals and specialized dialysis practices. Not only do these plants take up a lot of space and energy, but the water can only be used once as it disappears as waste water following dialysis. Based on a one-year time frame and 90,000 patients in Germany, over 1.7 million cubic meters of highly purified water are needed, without even taking the lost RO water into account.

Based on an approach which has never been applied to dialysis in the past, a procedure is being developed in the Department of Extracorporeal Immunomodulation that facilitates the regeneration of used dialysis water and could therefore completely change the huge problem of water dependability affecting the use of dialysis today. This procedure draws on the concept of freeze concentration used in the beverage industry and is based on the principle that the crystal lattice structure of frozen water excludes any previously dissolved foreign substances. As part of an automatable cycle, the procedure enables contaminated dialysate to be separated into pure water and a small residual volume containing impurities. This residual volume may arise from the patient’s regular liquid intake, removing the dialysis’ dependency on a pure water supply and making entirely mobile solutions conceivable. The fact that this separation occurs regardless of substance properties such as solubility, polarity, size, density, etc. is hugely beneficial compared with all conventional filter-based procedures, which do not demonstrate a sufficient filter capacity, especially for urea.

The procedure is currently being patented and an automated solution is undergoing development. This technical solution will then be used to carry out extensive investigations to specify process parameters that can later be used when working towards the initial clinical application. Notable industrial companies have already shown an interest in the procedure despite its early stage of development.

1 The wash column is central to automating the cryoprocess.
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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UNITS

MOLECULAR BIOTECHNOLOGY UNIT

The Molecular Biotechnology Unit develops and establishes analysis and model systems for use in cellular and molecular biology. This involves cell-based assays, gene expression analyses, immunological and protein-chemistry methods, sophisticated cell culture models and animal experiment approaches. In the area of preclinical development, the unit is able to conduct a series of cell-based tests to characterize substances with regard to efficacy, toxicology and transport. Furthermore, in collaboration with the department’s analytical laboratory, pharmacokinetic parameters are determined in vivo and the effectiveness of small molecules and protein drugs are investigated in respective disease models. The unit is also able to establish new animal models to investigate enzyme functions in the organism. Beyond this, it assists with drug development in terms of regulatory preclinical practice.

PROTEIN AND DRUG BIOCHEMISTRY UNIT

The Protein and Drug Biochemistry Unit has extensive experience in the purification of target proteins and their enzymatic characterization. Besides traditional protein chromatography procedures, protein chemical methods are also used, e.g. spectroscopic and crystallographic methods for analyzing structure and enzyme-kinetic effect. The unit specializes in the humanization of antibodies to manufacture protein drugs right up to their semi-preparative extraction. The subsequent structure-activity analysis and structure-based molecular optimization round off the unit’s portfolio.

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DRUG DESIGN AND ANALYTICAL CHEMISTRY UNIT

The service portfolio offered by the Drug Design and Analytical Chemistry Unit covers the entire spectrum of medicinal chemistry and analytics required to identify potential new drug candidates from the field of “small molecules” and develop them into clinical candidates.

By using computational procedures, potential new target molecules are first designed in silico and evaluated as to their efficacy on the target protein. Once this stage is complete, synthesis and real testing on the isolated target protein can then be carried out. The unit is also able to provide analytical assistance to drug development in preclinical and clinical trials. Respective parameters can be pursued using HPLC-coupled mass-spectrometry methods. These investigations can also be conducted in line with regulatory requirements (GLP).

Moreover, biophysical methods such as isothermal titration calorimetry and surface plasmon resonance spectroscopy are drawn upon to characterize binding behavior. Biological assays are developed and validated together with the other units, allowing the success of new types of treatment to be monitored using biomarkers.

PROTEIN MISFOLDING DISEASES UNIT

More than 300,000 new cases of amyloidoses are recorded in Germany every year. The diseases are caused by abnormally modified proteins being deposited in the body, usually in intercellular spaces. These insoluble protein fibrils, referred to as amyloids, damage not only the nervous system but also internal organs such as the heart, liver, kidneys, spleen or gastrointestinal tract and, in severe cases, also lead to their loss of function.

The Protein Misfolding Diseases unit carries out research into the impact of protein post-translational modifications and their influence on the emergence and prevention of amyloid diseases. To be able to detect pathogenic modifications using immunological assays, amyloid proteins are first expressed, purified and made to aggregate in vitro. Monoclonal antibodies are then produced and tested as therapeutic agents. The aim here is to develop personalized treatments in the form of antibodies.

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Neurodegenerative diseases are characterized by the progressive loss of brain substance. The degeneration of nerve cells coincides with the development of dementia, i.e. a qualitative and quantitative decline of brain cognitive performance. Due to the rise of life expectancy, dementia, especially Alzheimer’s Disease (AD), will pose a major challenge to our health systems in the decades to come. Despite the fact that some medication is available to relieve the symptoms of such diseases, no curative therapy is currently available.

The majority of neurodegenerative diseases is caused by a misfolding of proteins. This structural modification results in an aggregation that damages the surrounding tissue and nerve cells causing them to die off. An effective therapy has to prevent the peptides from aggregation and / or to accelerate the decomposition of these proteins. One way of triggering the degradation of the misfolded proteins is to apply antibodies which specifically target these non-natural proteins. The antibodies and misfolded amyloid peptides form complexes which are recognized and degraded by immune cells. One key aim of such approaches is to identify antibodies which only bind to misfolded, toxic material and which do not display any side activity to bind physiologically active peptides or proteins.

Therefore, our research focuses on so-called posttranslational modifications that are causally related to the development of the disease. Such modifications include, for instance, nitration, phosphorylation and the formation of isoaspartate. The project aims to generate and test antibodies which are highly specific to modified amyloid peptides. The most promising candidates will be selected from several different molecules and prepared for human use.
DETERMINATION OF PHARMACOKINETIC PARAMETERS OF SMALL MOLECULES

A comprehensive characterization of physico-chemical, cell-biological and pharmacokinetic properties of small molecules are prerequisite for their preclinical development. This process is required for the application of efficacious, safe and well-tolerated molecules in human subjects later during clinical development. Important steps during preclinics are investigations on liberation, absorption, distribution, metabolism and excretion (L-ADME parameters) in animal models. Here, information on exposure, bioavailability and terminal half-life will be collected. These data serve as decision points for selecting preclinical candidates or are used for optimization, e.g. bioavailability of an already selected candidate, by formulation development.

The Department of Drug Design and Target Validation at Fraunhofer IZI develops new molecular therapies for neurodegenerative and inflammatory disorders. The department’s strategy includes identifying novel drug target and testing novel therapies. For characterizing new small molecule classes, a catheter-based rat model for analyzing pharmacokinetics of such compounds has been established by the Molecular Biotechnology unit. The model is comprised of surgical application of a catheter in the jugular vein (V. jugularis) and in the carotid artery (A. carotis communis), respectively. Using this method, it is possible to obtain complete compound profiles from a single animal, which avoids inter-individual variations, e.g. when using mice. In addition, a close collaboration with the Drug Design and Analytical Chemistry unit enables rapid determination of compounds concentrations in blood samples by LC-MS.

The applied method is being used successfully within the Department of Drug Design and Target Validation, e.g. for own projects, such as the development of novel inhibitors for alternative beta-secretases or the development of novel inhibitors for the treatment of periodontitis. It is also requested and used by partners from industry and academia.

1|2 Mass spectrometry analysis to determine the concentration of the active ingredient in the organism (A).

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BROADENING THE CHEMICAL SPACE OF METAL BINDING GROUPS

A whole spectrum of target enzymes seen to be of medical interest contain a metal ion in their active site that is involved in the catalysis of the corresponding reaction. These metal ions usually present a starting point for the development of new drugs as the principal affinity of the respective inhibitor often emerges as the result of the medicinal substance binding to these metals. As however, until now, only very few active metal binding groups have been described in the literature, which then often do not block the actual target enzyme selectively but also other metal-dependent enzymes, the development of highly promising approaches often failed. Due to cross-reactivities within the enzyme class, matrix-metallo-protease inhibitors, for instance, were not pursued further despite years of intensive research.

A new computational chemistry approach has been developed in the Drug Design and Analytical Chemistry Unit that represents a combination of semi-empirical and quantum chemical methods alongside ligand- and structure-based approaches. Based on these complex calculations, it is now possible to significantly expand the chemical space of metal binding groups. Fragments discovered here are adapted for the respective application and constitute completely new chemical classes of molecules for future medicinal-chemical development. In the case of one particular metal-dependent acyltransferase, for example, alongside the four metal binders already known, another six new and just as active compound classes were able to be identified and pursued further.

As they had never been described in the past, they have now expanded the patent portfolio of the Department of Drug Design and Target Validation. The approach depicted here is currently being modified and adapted to the molecular properties of another target protein from the Astazine family. The aim is to avoid the possible adverse effects of potential new drugs described in the literature for the metal binding groups utilized so far.

1 View of the active site of Meprin β, a possible target enzyme involved in various fibrotic diseases. The graphic shows catalytically active zinc with the coordinating amino acids and a water molecule as the 4th ligand.
THE DEPARTMENT AT A GLANCE

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

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

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

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

CORE COMPETENCIES

- Point-of-care
- In vitro diagnostics
- Automation
- Assay development
- Device development
- Process automation

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UNITS

LABORATORY AND PROCESS AUTOMATION UNIT

This unit provides solutions for the automation of complex processes in biomedicine and biotechnology. The workflow in cell culture, cell expansion and monitoring, as usually done in the lab, forms the basis of analysis. The aim of all automation approaches is to standardize complex workflows and enhance efficiency as well as the quality of cell products.

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BIOMOLECULAR NANOSTRUCTURES AND MEASUREMENT TECHNOLOGY UNIT

The unit carries out research and development for the analysis of biomolecular interfaces and higher-order electronic effects. We focus on applications for point-of-care testing, however applications in a laboratory environment are also included. The unit covers a broad range of microscopy techniques including high-resolution optics, electronic and atomic forces microscopy, as well as THz spectroscopy.

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BIOMIMETIC FUNCTIONAL MATERIALS UNIT

The unit develops technologies and solutions for fast immunoassays. Homogeneous assays with an affordable electrochemical readout system are one focus, but also innovations of mature technologies: The hydrophilic surface coating for plastic disposables TruContact® minimizes antibody and sample consumption as well as unspecific protein binding in ELISA. “Smart” dry reagents tailored to the customer offer not only a high level of storage stability, but also added functionalities such as adhesion, transparency, slow-release kinetics or desiccation protection. Biomimetic electrochemical sensors, functionalized with artificial binding molecules (MIPs, “plastic antibodies”), offer new analytical options if antibodies are not available or desired.

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IVD PLATFORM / POC TECHNOLOGIES UNIT

The unit develops procedures and devices for various point-of-care applications. Based on miniaturized lab automation using microfluidics and biosensors, application-related, on-site solutions are developed for use in medical and non-medical fields. Among other things, an in vitro diagnostics platform (ivD platform) is available for this purpose, which can be adapted to different diagnostic tests depending on the matter at hand. Besides developing new diagnostic procedures, the unit offers customers and partners the opportunity to transfer existing tests (e.g. ELISAs, DNA microarrays, etc.) to the ivD platform. It also offers test optimization and technical verification, right through to authorization. The platform is open to numerous biomarkers and offers customers a fast way of moving from the biomarker to the actual product.

Current activities are focused around processing and detecting microbial samples (infection diagnostics, hygiene) and characterizing antibiotic resistances besides detecting specific nucleic acids in blood and other body fluids.

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NEW RAPID ANTIBIOTICS TEST: BETTER TREATMENT FOR DIABETIC FOOT ULCERS

People with type 2 diabetes often suffer from poorly-healing infected wounds on their feet. Using existing methods, however, it takes two days to grow a bacterial culture used to identify the pathogens infecting the wound and their antibiotic resistance – and thus to find an effective antibiotic. With the help of a new rapid test developed by Fraunhofer researchers, it will take just one hour to obtain this information in future.

Almost a thousand people are diagnosed with diabetes every day in Germany – more than 90 percent of them have type 2 diabetes. And the number of people developing the condition is rising both in Europe and worldwide. Type 2 diabetes can lead to numerous comorbidities, including hyperglycemia-induced damage to nerve cells. Affected patients lose feeling in their extremities and often develop skin ulcers that take a long time to heal, if at all. These wounds frequently become infected with various pathogens. Accordingly, doctors usually treat them with antibiotics. The problem is that not every antibiotic works against every pathogen, and antibiotic resistance is becoming more common.

A new type of rapid test enables doctors to use the right antibiotic from the beginning. It was developed in the MIDARDI project by researchers from the Fraunhofer Institutes for Cell Therapy and Immunology, Department of Bioanalytics and Bioprocesses IZI-BB (Potsdam), and for Electronic Nano Systems ENAS (Chemnitz) together with the company BiFlow Systems GmbH and partners in India. “With our rapid test, it’s possible to determine within one hour which bacteria have infected the wound and what antibiotic resistance they have – allowing doctors to choose suitable antibiotics right from the start of the treatment,” (Dr. Harald Peter, Group Leader at Fraunhofer IZI-BB).

Instead of culturing bacteria in the lab and observing how they react to various antibiotics, the rapid test analyzes the DNA of the bacteria. The doctor takes a swab of the wound and puts the wound fluid on the input area of the roughly smartphone-sized cartridge. On the inside, the bacteria are extracted, and their DNA is exposed and dissected. A biosensor built into the cartridge contains special capture molecules, which form the matching counterparts to the DNA strands of the bacteria and the mutated DNA that causes defined resistance. If a strand of DNA matches a certain capture molecule, it binds to it, while the DNA strands on all other capture molecules are removed in a rinsing cycle. The illumination of the fluorescence-labeled bacterial DNA reveals what capture molecules the pathogen DNA has bonded to – allowing a rapid species and antibiotic resistance identification.

PROJECT FUNDING

1 Microfluidic cartridge for on-site analysis.
Photo © BiFlow Systems GmbH.
THE DEPARTMENT AT A GLANCE

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

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

CORE COMPETENCIES

- Lab-on-chip
- Microfluidics and systems
- Biobanks
- Rapid prototyping
- Biosensor technology
- Assay development
- Functionalized surfaces

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UNITS

MICROFLUIDIC CELL PROCESSING AND CELL ANALYTICS UNIT

This unit offers the application-related and customer-specific development of procedures and prototypes to process and manipulate demanding biological samples. It focuses in part on manipulating individual objects, e.g. the gentle and highly precise handling and sorting of single cells and particularly small cell samples in microfluidic chips. For more complicated tasks, this is combined with complementary manipulation procedures involving optical tweezers or microfluidic processes. In addition, the unit deals with the integration of sensor technology in microfluidic components to record key parameters relating to cells and other complex biological samples. In this area, the unit is developing powerful test systems for the assessment of blood compatibility of cardiovascular medical devices under highly controlled flow conditions.

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BIOMARKER VALIDATION AND ASSAY DEVELOPMENT UNIT

The group’s activities include the development of specific assays for detecting and quantifying analytes in different matrices. The platforms used include microarrays, ELISA, lateral flow systems and bead-based assays for life science, environmental and food analysis. In addition, physicochemical parameters such as kinetic constants (Kd) can be determined and the composition or modification of surfaces can be characterized. All techniques are continuously being further developed for customer-specific applications. These applications include systems biology projects, the kinetic analysis of antibodies and the quantification of specific markers in serum samples.

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MOLECULAR BIO-ENGINEERING UNIT

This unit converts natural biological processes into isolated artificial architectures and strategies which utilize new perspectives in applications of cellular structures, mechanisms and metabolisms. In former studies, for example, modified synthetic membrane proteins were used to fix extracellular entities. More recent studies deal with innovative immunodominant antigens taken from cDNA libraries of prokaryotic transcriptomes, which mainly consist of pathogens, besides the development and construction of antimicrobial peptides, especially synthetic and artificial peptides, within the scope of antibiotic resistances.

MICROSYSYEMS FOR IN VITRO CELL MODELS UNIT

The Microsystems for In Vitro Cell Models Unit develops customer-specific, efficient methods and prototypes for the cultivation, characterization and processing of demanding cell samples. The design and implementation of innovative concepts are based on the group’s comprehensive expertise in microreactors, microfluidics, sensor technology and functional polymer coatings, and on its know-how in cell biology, toxicology and bioanalytics. The interdisciplinary orientation of the research unit enables a well-founded and targeted advice as well as an efficient execution of the customer’s specific needs. Activities focus on (i) developing in vitro test methods for assessing the toxicity of drugs and chemicals based on organ-on-chip systems and relevant cell models, as well as (ii) establishing intelligent polymer coatings which allow the behavior of adherent cells on technical surfaces to be controlled.

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MICROARRAY AND BIOSENSOR TECHNOLOGY UNIT

Currently, the request for fast information generation is rapidly increasing, and this also applies to analytical questions about "WHAT" or "HOW MUCH" to draw conclusions about one’s own behavior.

The "interface problem" is a major obstacle wherever natural structures meet technical systems.

Another is the challenge to draw as much analytical information as possible from as little and as native material as possible.

The solution lies in the modification of the respective surfaces. Through defined (bio)chemical functionalization, e.g. by branched linkers or the application of thin films using biopolymer-based membranes or switchable hydrogel layers, surfaces with new properties or so-called intelligent surfaces are created. The technological implementation takes place both on geometric materials such as fibers and on planar carriers such as plates or chips. The treatable surfaces themselves vary from glasses and wafer materials to natural fibers and plastics.

The result is independent sensor elements (e.g. test strip-based PoNd) or biosensor-based analytic tools (e.g. cell and peptide chips), for which various questions from the fields of environmental analysis, food monitoring, herd management, process control or diagnostics can be used on site and enable immediate data evaluation and transmission.
DEPARTMENT OF A PHYSIOLOGICALLY RELEVANT TEST SYSTEM FOR THE IN VITRO DETECTION OF HEPATOTOXICITY IN HIGH THROUGHPUT (HEPATOTOX)

For evaluating the toxicity and biocompatibility of pharmaceuticals, chemicals and cosmetics, alternative methods to animal testing, i.e. in vitro test systems, will be the standard in the near future. Besides the ethical motivation, the time and cost required for animal models is pushing the development and establishment of such cell tests forward.

One difficulty in the evaluation of in vitro toxicity measurements of new substances is the measurement of meaningful parameters that actually provide information on the condition of the cells or tissue. As yet, endpoint analyses (cell staining, gene and protein expression) prevail, but adapting them individually to the questions at hand takes considerable effort.

In the “HepatoTox” project, an organ-on-chip system is being developed with regard to higher throughput and the use of relevant cell models. The microfluidic bioreactor ensures 1. physiological conditions for the long-term culture of primary-like liver cells in a 3D matrix, 2. the measurement of cell vitality in real-time by integrating optical oxygen sensor particles and 3. the parallel analysis of up to twelve independent conditions by upscaling the fluidic elements and automating the system. In combination with the use of physiologically relevant cell models (Prof. Küpper, B-TU), the organ-on-chip system will be validated with reference substances to evaluate the significance and performance of the measurement system.

In addition to the commercialization of the organ-on-chip system, the project aims at providing a service to chemical and pharmaceutical companies in accelerating the registration procedures of newly developed substances.

PROJECT FUNDING

This project is funded by the European Regional Development Fund and the Land of Brandenburg.

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PROJECT EXAMPLES

1 Organ-on-chip system for long-term cultivation of hepatocytes with integrated optical sensors for real-time measurement of cell vitality.
BIODETECTOR - INTEGRATED DETECTION SYSTEM FOR BIOLOGICAL CONTAMINATION IN FUELS

The aim of the project was to develop an integrated system for DNA-based detection of biological contamination in fuels with minimal user effort. The biological contamination of fuel is an important issue in all areas where large amounts of fuel are needed or where fuel is stored over a long period of time, e.g. in transportation (freight and passenger transport, aviation) but also in the leisure sector e.g. boat engines and in agriculture (tractors and diesel tanks). The danger of clogged pipes by bacteria or fungi is very high. More than 100 different bacteria, yeasts and fungi are known to cause contamination and form bio-sludge in fuels. *Hormoconis resinae*, the so-called "diesel bug" or "kerosene fungus", is a so-called lead organism. It represents with 70-90% the most frequently occurring organism in contaminated fuels. Microorganisms are not only dangerous because they clog pipes and filters, but are also the cause of corrosion in fuel tanks.

Together with the expertise of the project partners M2-Automation and the Federal Institute for Materials Research and Testing (Department of Biological Materials Damage and Reference Organisms), researchers at Fraunhofer IZI-BB have developed a system that is capable of meeting the necessary requirements from sampling to sample preparation and detection.

The new method is characterized by:

- an integrated system solution
- acquisition with minimal sample preparation
- a timely detection at the place of sampling e.g. at the airport with presentation of the results and resulting recommendations for action
- the simultaneous detection of several relevant organisms (multiplexing)
- minimal user effort

Compared to the immunological methods already on the market, the new technology is more specific, faster and more sensitive. At the same time, the method enables the detection of a broad spectrum of microorganisms that are important for the contamination and degradation of fuel. The method can be transferred to other (viscous) liquids such as lubricating oils and paints.

1 Contaminated fuel. Photo © BAM.
2 Added fuel filter. Photo © BAM.
LOCATION POTSDAM-GOLM, GERMANY

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

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

The development, synthesis and also transfer of functional nucleic acids such as aptamers into market-relevant applications are just as much a focus as the analysis of cold-adapted snow algae in extremophile research. The latter of these are being used to extract high-quality substances such as antioxidants or fatty acids and are being manufactured in photobioreactors. The CCCryo culture collection as a unique bioresource can be used by academic and private sector interested parties.
UNITS

CELL-FREE PROTEIN SYNTHESIS UNIT

The unit researches and develops systems for the cell-free synthesis of recombinant proteins. A special focus lies on characterizing, modifying and examining the functions of cell-free manufactured proteins, with particular emphasis on ion channels, glycoproteins and antibody formats. Quick and affordable target-protein synthesis is ensured as only the constituents of the cells are used. The use of eukaryotic cell lysates also allows the synthesis of post-translationally modified proteins. Beyond this, position-specific labeling enables proteins to be specifically modified, changing and optimizing their properties, e.g. through the introduction of polymeric groups. By introducing fluorescent groups at selected positions, membrane proteins in particular can be measured, functionally characterized and analyzed with an eye to identifying new binding molecules.

EUKARYOTIC LYSATES UNIT

The unit develops cultivation systems of eukaryotic cell lines for the production of translational lysates for protein synthesis. In this respect, the testing of cell lines for their in vitro expression capabilities is of the highest interest. Furthermore, the unit continues to develop and optimize cell-free eukaryotic translation systems and investigates the influence of fermentation, cell disruption, and transcriptional and translational components on the productivity of the lysates. Based on this, the synthesis of proteins can be carried out in cell-free systems under the optimal conditions for the respective protein. The optimal synthesis conditions are protein-specific and are determined in evaluation studies. On request, protein syntheses can also be carried out under GLP conditions.

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EXTREMOPHILE RESEARCH & BIOBANK CCCRYO UNIT

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

FUNCTIONAL NUCLEIC ACIDS – APTAMERS UNIT

The Functional Nucleic Acids – Aptamers Unit aims at developing new innovative products on the basis of aptamers. This goal comprises the generation, synthesis and functionalization of aptamers as well as the integration in diverse applications. The unit thereby seeks a close collaboration with the industry and academic institutes. Primarily, aptamers are short, single-stranded DNA and RNA molecules with the particular feature of binding high-affine and high-specific a target molecule such as antibodies. The very broad capabilities of aptamers as binding molecules are used in analytical, diagnostic and therapeutic applications. A focus is on the generation of new aptamers by using an automatic in vitro selection process as well as a monitoring and managing process. Additionally, the unit develops of aptamer-based detection methods such as lateral flow assays or so-called aptasensors.

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APTAMER-BASED LATERAL FLOW RAPID TEST FOR DIAGNOSING ANTIBIOTIC RESISTANCES (ALF TEST)

The number of diseases caused by antibiotic-resistant bacteria is increasing around the globe: In 2005 in the European Union alone, around 50,000 people died from infections with resistant bacteria, while around 3 million people became infected. By 2050, the mortality rate is expected to be ten times this figure. Particularly multidrug-resistant Gram-negative bacteria (MDRGN) are becoming worryingly dangerous. It is vital that patients are diagnosed quickly and reliably in order to treat and isolate them effectively.

In Germany, around 20 million patients are treated in hospital every year. Due to the sharp increase of MDRGN infections, the Deutsche Stiftung Patientenschutz, an organization which represents the interests of the seriously ill, care recipients and end-of-life patients in Germany, is calling for all hospital patients to be screened upon being admitted to hospital. In addition to this, infected patients in particular are to be screened at least weekly.

The aim of this collaboration project is to conduct research into a new kind of lateral flow rapid test for detecting antibiotic-resistant bacteria. The rapid test is based on aptamers, i.e. short, single-stranded DNA or RNA nucleic acids, and is designed to detect bacteria within an hour without the need for further devices or specialist expertise. Patients are tested for the carbapenemases (bacterial enzymes) of the most common hospital infections. The rapid test will help prevent the spread of MDRGN bacteria, improve treatment and reduce the use of antibiotics. Once the project has ended, the initial aim will be to market the rapid test for high-risk patients.

PROJECT FUNDING

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CENTRAL FACILITIES AND SERVICES
GLP TEST FACILITY

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

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

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

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

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

BIOPHARMACEUTICALS

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

The clean rooms used for production of biopharmaceuticals cover a total area of 180 m² and comprise all clean room categories from D to A. The use of single-use equipment and materials enables an easy adaption to new process requirements. The GMP facility can be used for different contract manufacturing processes for preclinical and clinical (Phase 1 / 2) test samples as well as for process or instrument validation projects under consideration of special customer requests. The standard equipment can be easily adapted for new products.

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

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

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WHY ARE GLP AND GMP IMPORTANT?

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

ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPS)

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

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 macromolecules 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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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

CONTACT

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RIBOLUTION BIOMARKER CENTER

Over the past few years, the Fraunhofer Future Foundation has supported the RIBOLUTION project consortium, which takes an innovative approach to identifying new biomarkers for modern diagnostic solutions. The RIBOLUTION Biomarker Center was set up as part of a close cooperation involving five Fraunhofer institutes and several universities. It was opened on April 26, 2016, at the Fraunhofer Institute for Cell Therapy and Immunology IZI in Leipzig.

At the RIBOLUTION Biomarker Center, novel biomarkers are identified based on ribonucleic acids and developed through to clinical "proof of concept" with the aid of selected patient cohorts. At present, activities are primarily focused on development programs in the areas of prostate cancer, chronic obstructive pulmonary disease (COPD) and infectious diseases.

BIOMARKER SCREENING AND VALIDATION

By integrating state-of-the-art genomic analysis methods such as next-generation sequencing (NGS) using our own bioinformatical data analysis methods developed in house, the RIBOLUTION Biomarker Center is able to identify biomarkers and develop new diagnostic tests at the highest technological level:

- Illumina HiSeq and Miseq: Ultra-high-throughput sequencing platforms
- Hamilton Microlab STARlet / STARplus: Fully automated preparation of samples for sequencing and fully automated extraction and purification of nucleic acids
- Agilent microarray scanner
- EMD: Quality and quantity analyses of minimal amounts of nucleic acids with high sensitivity; developed by Fraunhofer FIT
- QIAcube: Semi-automated extraction and purification of nucleic acids
- RIBOT: Novel procedure for the automated validation of biomarkers in high-throughput based on complex interactions between actuator engineering and media to be dispensed; developed by Fraunhofer IPA
The highest quality standards are defined and implemented from start to finish, which increases the intrinsic value of the obtained data and lays the foundations for the implementation of a quality management system pursuant to DIN ISO 13485, which will become necessary as the project progresses.

New biomarkers are identified and validated using bioinformatical methods. This includes designing custom expression microarrays and analyzing expression microarray data. A proprietary data management system has been developed to store and supply all clinical and experimental data and is used to manage the extensive biobank which has emerged in the RIBOLUTION project.

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BIO-NANOTECHNOLOGY APPLICATION LABORATORY (BNAL)

The Bio-Nanotechnology Application Laboratory (BNAL) in Leipzig represents a research infrastructure jointly run by Fraunhofer IZI and Fraunhofer IKTS. With this laboratory, both institutes are opening up new fields of application in biomedicine related to various nanotechnologies.

State-of-the-art equipment allows biological and medical issues to be handled in an interdisciplinary manner. BNAL provides research and development services from fundamental biomedical research by process development up to the development and validation of innovative technologies and system solutions.

Biological and medical expertise at Fraunhofer IZI (e.g. oncology, chronic inflammatory diseases and neurodegenerative diseases) in combination with established analysis methods for material diagnostics at Fraunhofer IKTS enable the development of new diagnostic and therapeutic technologies and procedures.

IMAGING PROCEDURES

- Optical coherence tomography: Uses near-infrared light to depict the internal and surface structures of various materials in high resolution.
- Multi-acousto-scope: The combination of three microscopy techniques paves the way to innovative new examination strategies.

CELL CHARACTERIZATION AND CLASSIFICATION

- Diagnosis and mapping for cell biology studies: Non-intrusive way of delivering high-resolution, geometric information from the inside of test objects.
- Ultrasound broadband spectroscopy system: This procedure has long been used in the medical diagnosis of cell tissues, biological materials and in the analysis of fluid media. It mainly identifies acoustic and mechanical properties of substances.
- High-throughput flow cytometry: Rapid, multiplex, high-throughput screening of cells and beads in suspension.
- Fluorescence relaxation for characterizing cells in flow cytometry as a new, label-free procedure that will also be used to characterize cell therapeutic agents and which will be tested on a BD Influx high-throughput cell sorter.
SURFACE STERILIZATION AND MODIFICATION

- Electron beam dosimeter: Dose measurement of high energy radiation (e.g. gamma or electron radiation) on even on the different positions of bent 3D free-form surfaces.
- System for electron irradiation of surfaces: Sterilization of package / surfaces, inactivation of microorganisms for vaccine production or targeted adjustment of material properties by means of electron irradiation.

NANOTECHNOLOGY

- Droplet digital PCR system: PCR-based, absolute quantification of microbial / viral or eukaryotic DNA / RNA as well as precise detection of low genome copy numbers.
- Zetasizer: Determination of particle and molecule sizes, e.g. for characterizing recombinant proteins, micelles and nanoparticles.
- Micro-spotter unit: Automated dosing of tiny quantities of liquid (e.g. biological or organic solutions, or solutions containing nanoparticles) on a broad range of different surfaces for the production of microarrays.
- Hot-embossing system: Production-relevant manufacturing of nanostructured surfaces on glass and polymer surfaces.

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LOCATIONS
GERMANY

Headquarter
Leipzig, Saxony

Branch Bioanalytics and Bioprocesses
Potsdam-Golm, Brandenburg

Department of Drug Design and Target Validation
Halle (Saale), Saxony-Anhalt

Department of Extracorporeal Immunomodulation
Rostock, Mecklenburg-Western Pomerania

Branch Lab Translational Cell Therapy
Hannover, Lower Saxony

Project Center Microelectronic and Optical System for Biomedicine
Erfurt, Thuringia

SOUTH KOREA

JLCI – Joint Laboratory of Chonnam National University Hospital Hwasun in collaboration with Fraunhofer IZI
Gwangju, Jeollanam-do
Completed in April 2008, the main building boasts extensive laboratory capacities for conducting molecular and cell-biological work. An extensive immunohistochemistry laboratory, an isotope laboratory, a quality control laboratory with qualified equipment, as well as cyro-storage capacities also make up the institute's facilities.

The research infrastructure at the headquarters is complemented by various special facilities found in the extension buildings, which were opened in 2013 and 2015 (e.g. imaging units, laboratories for experimental medicine, a S3 laboratory, and clean-room facilities).

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

The business units Cell and Gene Therapy, Drugs and Diagnostics are primarily based in Leipzig. Biopharmaceutical products for clinical trials are manufactured in line with Good Manufacturing Practice (GMP) in the institute's clean-room facilities, which cover a total area of 1 000 m².
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.
The Department of Drug Design and Target Validation develops new molecular therapies for neurodegenerative and inflammatory diseases. The department's expertise is based on an in depth pharma-like understanding of scientific work and a long-lasting experience in the field of drug development.

This profile encompasses the identification of new target proteins by analyzing putative pathologic post-translational modifications, the misfolding of proteins and the formation of pathological aggregates. Based on these new strategies the department develops and tests small molecules as well as biological agents (biologics). This research is complemented by the design of new assays for the identification and diagnostic application of biomarkers aiming at monitoring the course of the disease and its therapy.

The department’s expertise also expands to the generation of pharmacologically relevant in vitro and in vivo models. Besides state-of-the-art methods for peptide synthesis and protein analytics (MALDI-TOF and LC-MS), the department commands a wide range of biophysical methods to characterize therapeutically relevant physiological pathways, their key proteins as well as cell-based and pharmacologic models for the characterization of new chemical and biological drug candidates.

DEPARTMENT OF DRUG DESIGN AND TARGET VALIDATION
HALLE (SAALE), SAXONY-ANHALT, GERMANY

The Department of Drug Design and Target Validation develops new molecular therapies for neurodegenerative and inflammatory diseases. The department's expertise is based on an in depth pharma-like understanding of scientific work and a long-lasting experience in the field of drug development.

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FACTS

- Address: Weinbergweg 22, 06120 Halle (Saale), Germany
- Usable area: 1 300 m²
- Employees: 68
- Focal areas: Biochemistry, pharmacology, drug development, analytics

MANAGEMENT

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Fraunhofer IZI Annual Report 2019
The department focuses on the development and evaluation of extracorporeal (outside the body) organ-supporting technologies with a particular emphasis on supporting the immune system.

The department offers the full range of preclinical and clinical analyses of extracorporeal technologies on the basis of a broad spectrum of in vitro simulations, small and large animal models as well as a powerful clinical study network for in- and outpatients. Moreover, the group offers self-developed unique analytic and diagnostic devices including an ex situ intestine model, a cell sensor and novel protein assays.

**FACTS**

- Address: Schillingallee 68, 18057 Rostock, Germany
- Usable area: 700 m²
- Employees: 32
- Focal areas: Organ-supporting technologies, clinical trials

**MANAGEMENT**

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The Branch Lab Translational Cell Therapy develops and validates cell-based advanced therapy medicinal products (ATMPs). To do this, it conducts translational research and develops GMP-compliant manufacturing protocols for cell therapeutics at the interface to preclinical development right through to their transfer into clinical trials. Cell and genetic engineering methods and strategies are implemented and optimized here to specifically manufacture killer lymphocytes and their subpopulations. The ability to overcome so-called tumor immune escape mechanisms in cancer cells is key here. This is achieved by using activated and genetically modified effector cells together with checkpoint inhibitors and stimulating immune cells. These cell therapies boost immune surveillance and strengthen the elimination of resistant cancer cells as well as their malignant precursor cells (so-called tumor stem cells).

Another focus of development lies in optimizing the transduction capacity of effector cells using chimeric antigen receptors (CARs) in order to increase cytotoxicity to malignant cells. To do this, human effector cells are separated following lymphapheresis by means of GMP-suitable, fully automated, closed-system production, genetically modified as necessary and expanded as part of clinical upscaling.

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

INVOLVED FRAUNHOFER INSTITUTES

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

FACTS

- Address: Herman-Hollerith-Straße 3, 99099 Erfurt, Germany

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Since 2010, Fraunhofer IZI has maintained a close cooperation with Chonnam National University Hospital Hwasun (CNUHH) in several areas. With 700 beds, the CNUHH is one of the largest university hospitals specialized in the treatment of cancer in South Korea. A vibrant biotech and medtech industry has established itself in the local area. The JLCI facilitates the collaboration with external partners from academia and industry in Asia. For example the Fraunhofer IZI’s ligand development group is using the regular access to fresh tumor materials from patients to identify tumor binding peptides, which already have been validated in tumor models. The laboratory management is oriented at the standards and rules of the Fraunhofer-Gesellschaft. This shall guarantee a common basis when dealing with patents and contractual matters.

The JLCI was financed until 2017 by the Korean Ministry of Education, Science and Technology in Gwangju, Jeollanam-do, South Korea, as part of an initiative to strengthen international cooperation. Since 2018, additional funds have been authorized by the provincial government of Jeollanam-do and the district of Hwasun gun in order to facilitate stronger connections within the industry and with other research institutes in Korea and Germany through professional business development.

Various projects have been conducted to date at the JLCI, e.g. in the field of senescence and cancer research, also as part of funding measures associated with the Federal Ministry of Economics and Technology’s Central Innovation Program for SMEs. Several Fraunhofer IZI delegations have already taken part in conferences and research stays in Korea and a number of Korean colleagues have also worked at Fraunhofer IZI. The joint research work is documented in many joint publications. German-Korean symposia have so far taken place on an annually rotating basis.

JLCI – JOINT LABORATORY OF CHONNAM NATIONAL UNIVERSITY HOSPITAL HWASUN IN COLLABORATION WITH FRAUNHOFER IZI
GWANGJU, JEOLLANAM-DO, SOUTH KOREA

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CONVENTIONS AND CONFERENCES

1. Brandenburger Versorgungsforschungskongress, Neuruppin, Germany, September 13, 2019

13th Vaccine Congress, Bangkok, Thailand, September 15–18, 2019

15th German Conference on Cheminformatics, Mainz, Germany, November 3–5, 2019

15th Leipzig Research Festival for Life Sciences, Leipzig, Germany, January 18, 2019

18th Congress of the Japanese Society for Regenerative Medicine, Kobe, Japan, March 21–23, 2019

19. Jahrestagung der Arbeitsgemeinschaft Akkreditierter Laboratorien, Berlin, Germany, September 13–14, 2019

1st Bonn Nanobody Symposium, Bonn, Germany, September 5–6, 2019

20th International Symposium on Albumin Dialysis, Rostock, Germany, September 6–8, 2019

23. Phytopharmaka Symposium 2019, Mannheim, Germany, October 9–10, 2019

24th Annual Meeting of the RNA Society, Krakow, Poland, June 11–16, 2019

29th Annual Meeting of the DGfZ »Visions in Cytometry«, Berlin, Germany, September 25–27, 2019

29th Annual Meeting of the Society for Virology, Düsseldorf, Germany, March 20–23, 2019

29th European Congress of Clinical Microbiology & Infectious Diseases, Amsterdam, The Netherlands, April 13–16, 2019

2nd Autumn Meeting German Society for Extracellular Vesicles, Freising, Germany, November 28–29, 2019

2nd European Biosensor Symposium EBS2019, Florence, Italy, February 18–21, 2019

3rd KDDF Global C&D Tech Fair, Seoul, South Korea, February 20, 2019

33rd EFFoST International Conference, Rotterdam, The Netherlands, November 12–14, 2019

4. Forum Veterinärdiagnostik, Berlin, Germany, May 9, 2019

4. Münchner Point-of-Care Testing Symposium, Munich, Germany, March 11–13, 2019


5. Forum Veterinärdiagnostik, Berlin, Germany, September 24, 2019

5. International Symposium of the SFB 765 »Multivalency in Chemistry and Biology«, Berlin, Germany, September 30 – October 2, 2019

5. NutriAct-Jahrestagung, Potsdam, Germany, November 8, 2019

6. Update: Prädiktive molekularpathologische Diagnostik, Frankfurt am Main, Germany, October 11, 2019

7th European Congress of Virology (ECV) 2019, Rotterdam, The Netherlands, April 28 – May 1, 2019

9. Herbsttreffen der AG Molekularpathologie der Deutschen Gesellschaft für Pathologie e.V., Wiesloch, Germany, November 14–15, 2019

9th Alpbach Workshop on Affinity Proteomics, Alpbach, Austria, March 11–13, 2019

9th International Symposium on Recent Advances in Food Analysis, Prague, Czech Republic, November 5–8, 2019

Abschlussveranstaltung der Förderlinie »ProProfessur« des Landes Hessen, Gießen, Germany, November 21, 2019

AlpenFlow 2019. Österreichische Gesellschaft für Zytometrie, Bad Ischl, Austria, December 5–7, 2019

Analyseren, Kultivieren, Desinfizieren – Ein Anwenderblick auf neue Polymere und Oberflächen in der Biotechnologie, Potsdam, Germany, September 11, 2019

BfR-Symposium »Zoonosen und Lebensmittelsicherheit«, Berlin, Germany, November 4–5, 2019

Bio International Convention 2019, Philadelphia, USA, June 3–6, 2019

BioBilanz 2019, Berlin, Germany, January 24, 2019

BIOCHIP Berlin International Forum on BioChips and BioChip Solutions, Berlin, Germany, May 7–8, 2019

BIO-Europe®, Hamburg, Germany, November 11–13, 2019
BioJapan 2019, Yokohama, Japan, October 9–11, 2019
Biologische Transformation mit Schwerpunkt Bioökonomie, Berlin, Germany, September 26, 2019
Bionnale 2019, Berlin, Germany, May 7, 2019
BioProcess International European Summit 2019, Vienna, Austria, April 2–5, 2019
Biotech Showcase 2019, San Francisco, USA, January 7–10, 2019
Boehringer Ingelheim – Networking Reception, Berlin, Germany, September 30, 2019
Breath Summit 2019, Leicestershire, Great Britain, September 8–11, 2019
Cell & Gene Meeting on the Mediterranean, Barcelona, Spain, March 23–24, 2019
Cluster pitches – Klinik trifft Diagnostik, Henningsdorf, Germany, October 24, 2019
Clusterkonferenz Gesundheitswirtschaft Berlin-Brandenburg 2019, Potsdam, Germany, November 7, 2019
COMPAMED 2019, Düsseldorf, Germany, November 18–21, 2019
BioTech Showcase 2019, San Francisco, USA, January 7–10, 2019
Biologische Transformation mit Schwerpunkt Bioökonomie, Berlin, Germany, September 26, 2019
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Cluster pitches – Klinik trifft Diagnostik, Henningsdorf, Germany, October 24, 2019
Clusterkonferenz Gesundheitswirtschaft Berlin-Brandenburg 2019, Potsdam, Germany, November 7, 2019
COMPAMED 2019, Düsseldorf, Germany, November 18–21, 2019
CYTO 2019 – 34th Congress of the International Society for Advancement of Cytometry, Vancouver, Canada, June 22–26, 2019
Day of Intravital Microscopy, Marburg, Germany, November 25–26, 2019
Denkfabrik CDU – Fachforum 4 »Unser Europa für eine verlässliche Gesundheits- & Pflegeversorgung in Sachsen«, Dresden, Germany, May 17, 2019
deSE19 – Konferenz für ForschungssoftwareentwicklerInnen in Deutschland, Potsdam, Germany, June 4–6, 2019
DG-GT Theme Day »CAR-T cells and beyond«, Leipzig, Germany, September 16–17, 2019
DNA Mitteldeutschland, Leipzig, Germany, November 29, 2019
DNA Mitteldeutschland, Jena, Germany, May 23, 2019
EFRE.BB 21I27, Potsdam, Germany, October 1, 2019
EIT Health Matchmaking, Berlin, Germany, February 6–7, 2019
Fraunhofer-Symposium »Netzwert«, Munich, Germany, February 26–27, 2019
GE Healthcare Life Sciences Cell Therapy Insight, Leipzig, Germany, November 13, 2019
German Society for Extracellular Vesicles Annual Meeting, Frankfurt am Main, Germany, March 7–8, 2019
Global Expert Mission: UK-Germany Antimicrobial Resistance (AMR), Potsdam, Germany, May 20–24, 2019
GlycoBioTec 2019, Berlin, Germany, January 28–30, 2019
HEC 22 – 22nd Heart of Europe Bio-Crystallography Meeting 2019, Obergrub, Austria, September 12–14, 2019
In-cosmetics Global 2019, Paris, France, April 2–4, 2019
Innovationstag Mittelstand des BMWi 2019, Berlin, Germany, May 9, 2019
ISEV Annual Meeting, Kyoto, Japan, April 24–28, 2019
Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie, Berlin, Germany, October 11–14, 2019
Junior Scientist Symposium FLJ 2019, Jena, Germany, September 25–27, 2019
Kick-off Meeting RESTORE, Berlin, Germany, May 6, 2019
KI-Hub Sachsen »Wir bringen KI in die Anwendung«, Chemnitz, Germany, October 29, 2019
LABVOLUTION, Hannover, Germany, May 21–23, 2019
Lebensmittelsicherheit in Deutschland – was bleibt? Wie Lebensmittelverarbeitung die Inhaltsstoffe verändert, Potsdam-Rehbrücke, Germany, June 4, 2019
Life Science Forum Sachsen 2019 und Gesundheitsforum Healthy Saxony »Innovationen für die onkologische Versorgung«, Chemnitz, Germany, October 9, 2019
LSFM2019: The Light Sheet Microscopy Conference, Frankfurt am Main, Germany, December 4–6, 2019
MEDICA 2019, Düsseldorf, Germany, November 18–21, 2019
MMC 2019 – Microscience Microscopy Congress, Manchester, Great Britain, July 1–4, 2019
Network Event »Women in Oncology«, Berlin, Germany, November 27, 2019
New and Emerging Technologies 2019 »Biotech meets Medicine«, Potsdam-Golm, Germany, September 18–20, 2019
Phacilitate Cell and Gene Therapy World, Miami, USA, January 22–24, 2019

Potsdamer GründerTag 2019, Potsdam, Germany, June 13, 2019


Sondersitzung GESUNDHEIT: Antibiotikaresistenz, Berlin, Germany, October 17, 2019

Tag der Bioökonomie, Berlin, Germany, September 26, 2019

Tag der Immunforschung, Frankfurt am Main, Germany, June 19, 2019

»The product is the process – is it?« Quality aspects in the production of ATMP, Potsdam, Germany, November 12, 2019

Update Hämatologie / Onkologie, Hamburg, Germany, August 16–17, 2019

VIP+ Innovationstagung, Berlin, Germany, March 26, 2019
RESEARCH PARTNERS

AIT Austrian Institute of Technology, Vienna, Austria
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Aristotle University of Thessaloniki, Thessaloniki, Greece
Asociación de la Industria Navarra, Cordovilla, Spain
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Beuth University of Applied Sciences Berlin, Berlin, Germany
Bielefeld University, Bielefeld, Germany
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Brandenburg University of Applied Sciences, Brandenburg, Germany
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Charité – Universitätsmedizin Berlin, Berlin, Germany
Charles University, Prague, Czech Republic
Chonnam National University Hwasun Hospital, Hwasun, South Korea
Chonnam National University Medical School, Hwasun, South Korea
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Coburg University of Applied Sciences and Arts, Coburg, Germany
Competence Center for scalable data services and solutions ScADoS, Dresden / Leipzig, Germany
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Erasmus MC, Rotterdam, The Netherlands
Experimental and Clinical Research Center (ECRC), Berlin, Germany
FH Aachen University of Applied Sciences, Jülich, Germany
Flensburg University of Applied Sciences, Flensburg, Germany
Forschungszentrum Jülich, Jülich, Germany
Fraunhofer Institute for Applied Information Technology FIT, Sankt Augustin, Germany
Fraunhofer Institute for Applied Optics and Precision Engineering IOF, Jena, Germany
Fraunhofer Institute for Applied Polymer Research IAP, Potsdam, Germany
Fraunhofer Institute for Biomedical Engineering IBMT, St. Ingbert, Germany
Fraunhofer Institute for Ceramic Technologies and Systems IKTS, Dresden, Germany
Fraunhofer Institute for Chemical Technology ICT, Pfinztal, Germany
Fraunhofer Institute for Electronic Nano Systems ENAS, Chemnitz, Germany
Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB, Stuttgart, Germany
Fraunhofer Institute for Manufacturing Engineering and Automation IPA, Stuttgart, Germany
Fraunhofer Institute for Manufacturing Technology and Advanced Materials IFAM, Bremen, Germany
Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Frankfurt am Main; Aachen, Germany
Fraunhofer Institute for Organic Electronics, Electron Beam and Plasma Technology FEP, Dresden, Germany
Fraunhofer Institute for Photonic Microsystems IPMS, Dresden, Germany
Fraunhofer Institute for Process Engineering and Packaging IVV, Freising, Germany

Fraunhofer Institute for Reliability and Microintegration IZM, Berlin, Germany

Fraunhofer Institute for Telecommunications, Heinrich Hertz Institute, HHI, Berlin, Germany

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German Rheumatism Research Centre Berlin (DRFZ), Berlin, Germany

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Harvard Medical School, Boston, USA

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Heinrich Pette Institute, Leibniz Institute for Experimental Virology, Hamburg, Germany

Helios Hospital Berlin-Buch, Berlin, Germany

Helios Hospital Erfurt, Erfurt, Germany

Helmholtz Centre for Environmental Research GmbH – UFZ, Leipzig, Germany

Helmholtz Centre for Infection Research, Braunschweig, Germany

Helmholtz Centre Potsdam - GFZ German Research Centre for Geosciences, Potsdam, Germany

Helmholtz-Zentrum Geesthacht, Centre for Materials and Coastal Research (HZG), Teltow, Germany

Helmholtz Zentrum München German Research Center for Environmental Health, Munich, Germany

Hospital Chemnitz, Chemnitz, Germany

Hospital St. Elizabeth and St. Barbara, Halle (Saale), Germany

Hudson Institute of Medical Research, Melbourne, Australia

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Innovations for High Performance Microelectronics, Leibniz Institute for Innovative Microelectronics, Frankfurt (Oder), Germany

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Institute for Applied Informatics (InfAI), Leipzig, Germany

IMMS Institut für Mikroelektronik- und Mechatronik-Systeme gemeinnützige GmbH, Ilmenau, Germany

IRGIB Africa University, Cotonou, Benin

Jagiellonian University, Krakow, Poland

Julius Kühn Institute (JKI) Federal Research Centre for Cultivated Plants, Siebeldingen, Germany

Karolinska Institutet, Stockholm, Sweden

Kiel University (CAU), Kiel, Germany

KU Leuven, Leuven, Belgium

Leibniz Institute for Plasma Science and Technology (INP Greifswald), Greifswald, Germany

Leibniz Institute for Zoo and Wildlife Research (IZW), Berlin, Germany

Leibniz Institute of Surface Engineering, Leipzig, Germany
<table>
<thead>
<tr>
<th>Institution</th>
<th>Location</th>
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<tbody>
<tr>
<td>Leibniz Institute of Vegetable and Ornamental Crops (IZG),</td>
<td>Großbeeren, Germany</td>
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<td>Leibniz University Hannover,</td>
<td>Hannover, Germany</td>
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<td>Leipzig Heart Center, Leipzig,</td>
<td>Germany</td>
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<td>Leipzig University, Leipzig,</td>
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<td>Leipzig University of Applied Sciences (HTWK Leipzig),</td>
<td>Leipzig, Germany</td>
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<tr>
<td>Liverpool School of Tropical Medicine, Liverpool,</td>
<td>Great Britain</td>
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<td>Ludwig-Maximilians-Universität München, München, Germany</td>
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<td>Maastricht University, Maastricht, The Netherlands</td>
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<td>Mahidol University, Nakhon Pathom, Thailand</td>
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<td>Makerere University, Kampala, Uganda</td>
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<td>Manipal Academy of Higher Education, Manipal, India</td>
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<td>Marien Hospital Herne – Universitätsklinikum der Ruhr-Universität Bochum,</td>
<td>Herne, Germany</td>
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<td>Martin Luther University Halle-Wittenberg, Halle (Saale), Germany</td>
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<td>Max Delbrück Center for Molecular Medicine, Berlin, Germany</td>
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<td>Max Planck Institute for Molecular Genetics, Berlin, Germany</td>
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<td>Max Planck Institute of Colloids and Interfaces, Potsdam, Germany</td>
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<td>McGill University, Montreal, Canada</td>
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<td>McMaster University and St. Joseph's Healthcare, Hamilton, Canada</td>
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<td>MD Anderson Cancer Center, Houston, USA</td>
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<td>Multitel, Mons, Belgium</td>
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<td>National Autonomous University of Mexico, Ciudad de México, México</td>
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<td>National Institute for Standards and Technology (NIST), Gaithersburg, USA</td>
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<td>Newcastle University, Newcastle upon Tyne, Great Britain</td>
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<td>Oslo University Hospital, Oslo, Norway</td>
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<td>Ospedale San Raffaele S.r.l., Milan, Italy</td>
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<td>Otto von Guericke University Magdeburg, Magdeburg, Germany</td>
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<td>Paul Flechsig Institute of Brain Research, Leipzig, Germany</td>
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<td>Pilot Pflanzenöltechnologie Magdeburg e. V. (PPM), Magdeburg, Germany</td>
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<td>Potsdam Institute for Climate Impact Research, Potsdam, Germany</td>
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<td>Research Center Borstel, Leibniz Lung Center, Borstel, Germany</td>
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<td>Robert Koch Institute, Berlin, Germany</td>
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<td>Rostock University Medical Center, Rostock, Germany</td>
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<td>Ruhr-Universität Bochum (RUB), Bochum, Germany</td>
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<td>Rural Service Center of Rhineland-Palatinate, Bernkastel, Germany</td>
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<td>Saxony State Office for the Environment, Agriculture and Geology, Köllitsch, Germany</td>
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<td>Seoul National University, Seoul, South Korea</td>
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<td>Technical University of Applied Sciences Wildau, Wildau, Germany</td>
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<td>Universidade Federal do Rio de Janeiro – UFRJ, Rio de Janeiro, Brasil</td>
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<td>Universiti Putra Malaysia, Serdang, Malaysia</td>
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<td>University of Bern, Bern, Switzerland</td>
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<td>University of Bonn, Bonn, Germany</td>
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<td>University of California, Los Angeles; San Diego, USA</td>
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<td>University of Freiburg, Freiburg, Germany</td>
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<td>University of Graz, Graz, Austria</td>
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<td>University of Greifswald, Greifswald, Germany</td>
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<td>University of Innsbruck, Innsbruck, Austria</td>
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<td>University of Kassel, Kassel, Germany</td>
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<td>University of Leipzig Medical Center, Leipzig, Germany</td>
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<td>University of Padua, Padua, Italy</td>
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<td>University of Rostock, Rostock, Germany</td>
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<td>University of Veterinary Medicine Hannover, Foundation, Büsum, Germany</td>
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INDUSTRY PARTNERS

*2bind GmbH*, Regensburg, Germany

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Vaccinex Inc., Rochester, USA
Villeroy & Boch AG, Mettlach, Germany
Vita 34 AG, Geschäftsbereich BioPlanta, Leipzig, Germany

Vita34 AG, Leipzig, Germany

Vivoryon Therapeutics AG, Halle (Saale), Germany

We love apps, Erfurt, Germany

WISAG AG, Frankfurt am Main, Germany

Wrig Nanosystems GmbH, Leipzig, Germany

YUMAB GmbH, Braunschweig, Germany

Zellmechanik Dresden GmbH, Dresden, Germany
**Teaching Activities**

**Beuth University of Applied Sciences Berlin**

Selected aspects of biotechnology: Cell free protein synthesis (lecture), Dr. Stefan Kubick

Training in protein biochemistry (training), PD Dr. Harald Seitz

**Freie Universität Berlin**

Cell-free Synthesis of Membrane Proteins (seminar / training), Dr. Stefan Kubick

Membrane Proteins: Classification, Structure and Function (lecture), Dr. Stefan Kubick

Optical microscopy of the submicroscopic (course), PD Dr. Ralph Hözel, Eva-Maria Laux

**Hospital Chemnitz**

Advanced training for assistant doctors (seminar), PD Dr. Stephan Fricke

**Leipzig University**

Acute and chronic infection of the cardiovascular system (lecture), Prof. Dr. Dr. Andreas Oberbach

Bed Site teaching (seminar), Prof. Dr. Dr. Andreas Oberbach

Cardiosurgical emergencies (lecture), Prof. Dr. Dr. Andreas Oberbach

Drug analysis – Drug monitoring I (seminar), Dr. Mirko Buchholz

Drug analysis – Drug monitoring II (seminar), Dr. Mirko Buchholz

Experimental physics and its mathematical methods EP3 – optics and thermodynamics (lecture), Dr. Jörg Schnauß

Immunological internship, 6th semester human medicine (training), Dr. Dennis Löffler, Dr. Conny Blumert

International guidelines for drugs, EMA and FDA; strategies and methods for testing for immunotoxic effects of chemicals and drugs (lecture), Dr. Jörg Lehmann

Lab training molecular medicine / virology (training), PD Dr. Sebastian Ulbert, Dr. Jasmin Fertey

Molecular aspects of food allergy (lecture), Dr. Elke Ueberham

Molecular medicine / virology (lecture), PD Dr. Sebastian Ulbert

Molecular Nanotechnology (seminar), Dr. David M. Smith

Morphology and function of immunological cells and organs / basic functions of the immune system (lecture), Dr. Jörg Lehmann

Organic chemistry (training), Dr. Daniel Ramsbeck

Pharmaceutical biology / immunology (lecture), Dr. Jörg Lehmann

Preclinical in vitro and in vivo models for the detection and evaluation of immunotoxic effects of drugs (lecture), Sina Riemschneider

QSB4 autoimmunity and pathogenic immune reactions (course), Dr. Peter Ruschpler

QSB4 infectiology / immunology (lecture), Prof. Dr. Dr. Ulrike Köhl

Soft matter physics and biological physics (lecture / seminar), Dr. Jörg Schnauß, Dr. David M. Smith

Statistical learning (lecture), Dr. Kristin Reiche, Dr. David Petroff, Dr. Andreas Kühnapfel, Prof. Martin Bogdan

Surgical exercise (seminar), Prof. Dr. Dr. Andreas Oberbach

Therapy of heart failure (lecture), Prof. Dr. Dr. Andreas Oberbach

Transplantation and implantation of artificial heart (lecture), Prof. Dr. Dr. Andreas Oberbach

Vector-borne virus infection (lecture), PD Dr. Sebastian Ulbert

Virology (training), Dr. Lea Bayer, Dr. Thomas Grunwald

**Leipzig University Medicine**

POL-1 course (course), Dr. Yarúa Jaime

Training immunology (training), Dr. Yarúa Jaime, Kerstin Wenk
Leipzig University of Applied Sciences (HTWK Leipzig)

Biomedical imaging (lecture), Prof. Dr. Ulf-Dietrich Braumann
Bioreactors (lecture), Prof. Dr. Ulf-Dietrich Braumann
Image processing (lecture), Prof. Dr. Ulf-Dietrich Braumann
Imaging (lecture), Prof. Dr. Ulf-Dietrich Braumann
Microscopic imaging (lecture), Prof. Dr. Ulf-Dietrich Braumann, Dr. Sebastian Greiser
Microscopic image processing (lecture), Prof. Dr. Ulf-Dietrich Braumann
Production of recombinant proteins in a bioreactor using monoclonal antibodies as an example – Critical process parameters and control – GMP production (lecture), Dr. Maximilian Hoffmann

Stem cell biology (within bioreactors) (lecture), Dr. Claire Fabian

Martin Luther University Halle-Wittenberg

Animal Experimental Replacement Methods – Organ on a Chip (within the framework of the Colloquium on Animal Experimentation) (lecture), Dr. Claire Fabian
Applied cheminformatics for bioinformaticians (seminar), Dr. Mirko Buchholz, Christian Jäger
Lab Course on Vector Construction (training), PD Dr. Stephan Schilling
Molecular Biotechnology: Construction of Hosts and Vectors (lecture), PD Dr. Stephan Schilling
Non-curricular teaching (module supervision in the master program biochemistry / molecular biology for physicians) (training / seminar), Dr. Holger Cynis

Technical University of Berlin

Cell-free synthesis of membrane proteins (training), Dr. Stefan Kubick
Membrane proteins: Classification, structure and function (lecture), Dr. Stefan Kubick

University of Applied Sciences Zittau / Görlitz

GMP – Basic training (lecture), Dr. Maximilian Hoffmann
Production of recombinant proteins in a bioreactor using monoclonal antibodies as an example – Critical process parameters and control – GMP production (lecture), Dr. Maximilian Hoffmann

University of Potsdam

Applied limnology: Snow algae as an interesting bioresource for basic research and industrial bioproduction of algal metabolites (lecture), Dr. Thomas Leya
Cell-free Protein Synthesis (lecture / seminar), Dr. Stefan Kubick
Cell-free Synthesis of Membrane Proteins (training), Dr. Stefan Kubick
Immunobiological methods (seminar), PD Dr. Harald Seitz
EVALUATOR ACTIVITIES

ACS Applied Materials & Interfaces, Dr. Claus Duschl
Advances in Dairy Research, Dr. Jörg Lehmann
Alexander von Humboldt Foundation, Prof. Dr. Ulrike Köhl
Alzheimer’s Association, Dr. Holger Cynis
American Association for Cancer Research, Prof. Dr. Ulrike Köhl
Analytical Chemistry, Dr. Eva Ehrentreich-Förster
Arctic, Antarctic, and Alpine Research, Dr. Thomas Leya
Austrian Research Promotion Agency (FFG), Franziska Lange
AWIPEV Arctic Research Base, Dr. Thomas Leya
BMC Bioinformatics, Michael Rade
BMC Veterinary Research, Dr. Elke Ueberham
Clinical Science, Dr. Holger Cynis
Cytometry Part A, Prof. Dr. Attila Tőnök
Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), Dr. Eva Ehrentreich-Förster, Prof. Dr. Ulrike Köhl
Deutsche Krebshilfe, Prof. Dr. Ulrike Köhl
Emerging Microbes and Infections, PD Dr. Sebastian Ulbert
Engineering in Life Sciences, Dr. Stefan Kubick
European Society for Blood and Marrow Transplantation (EBMT), Prof. Dr. Ulrike Köhl
Faculty 1000, Dr. Jörg Lehmann
Frontiers in Aging Neuroscience, Dr. Holger Cynis
Future Virology, PD Dr. Sebastian Ulbert
German Center for Infection Research, PD Dr. Sebastian Ulbert
High-Tech Gründerfonds Bonn über das Steinbeis Transferzentrum, Dr. Mirko Buchholz
José Carreras Stiftung, Prof. Dr. Ulrike Köhl
Journal Blood Reviews, Prof. Dr. Ulrike Köhl
Journal Frontiers in Immunology, Prof. Dr. Ulrike Köhl
Journal Human Gene Therapy, Prof. Dr. Ulrike Köhl
Journal of Alzheimer’s Disease, PD Dr. Stephan Schilling
Journal of Clinical Microbiology, PD Dr. Sebastian Ulbert
Journal of Molecular Therapy, Prof. Dr. Ulrike Köhl
Journal of Proteomics, Prof. Dr. Stefan Kalkhof
Material Science and Engineering: C, Dr. Claus Duschl
Metabolic Brain Disease, PD Dr. Stephan Schilling
Molecular Biology Reports, Dr. Holger Cynis
Parasites & Vectors, PD Dr. Sebastian Ulbert
PLOS One, Dr. Thomas Grunwald, Dr. Jörg Lehmann, Prof. Dr. Dr. Andreas Oberbach
Scientific Reports, Prof. Dr. Stefan Kalkhof
SPIE Medical Imaging Conference, Prof. Dr. Ulf-Dietrich Braumann
The Journal of Thoracic and Cardiovascular Surgery, Prof. Dr. Dr. Andreas Oberbach
Vaccine, Dr. Thomas Grunwald
Vaccines, PD Dr. Sebastian Ulbert, Dr. Thomas Grunwald
Veterinary Immunology and Immunopathology, Dr. Jörg Lehmann
Viral Immunology, PD Dr. Sebastian Ulbert
ASSOCIATION MEMBERSHIPS

Alliance for Regenerative Medicine, Dr. Thomas Tradler MBA

Alumni der Leipziger Medizinischen Fakultät e. V. – ALM, PD Dr. Stephan Fricke

Alzheimer’s Association International Society to Advance Alzheimer’s Research and Treatment (ISTAART), Dr. Holger Cynis, PD Dr. Stephan Schilling

American Chemical Society (ACS), Christian Jäger, Dr. Mirko Buchholz, Dr. Daniel Ramsbeck

American Society for Mass Spectrometry, Prof. Dr. Stefan Kalkhof

biosaxony e.V., Dr. Thomas Tradler MBA

bbb – Biotechnologieverbund Berlin-Brandenburg e.V., Dr. Thomas Tradler MBA

btS – Biotechnologische Studenteninitiative e.V., Carolin Meier

Dachverband der Technologen/-innen und Analytiker/-innen in der Medizin Deutschland e.V., Ulrike Ehler...

DECHHEMA Gesellschaft für Chemische Technik und Biotechnologie e.V. (Society for Chemical Engineering and Biotechnology), Dr. Mirko Buchholz, Dr. Stefan Kubick

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Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e.V., Prof. Dr. Dr. Ulrike Köhl

Deutsche Gesellschaft für Medizinische Physik e.V., Prof. Dr. Ulf-Dietrich Braumann

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Dr. Thomas Grunwald,
PD Dr. Sebastian Ulbert

The Network for Pharma Solutions – NetPhaSol,
Dr. Marcus Menges

The RNA Society,
Dr. Sandy Tretbar

Tierärztliche Vereinigung für Tierschutz e.V.,
Dr. Vera Rieckmann

Zentrale Tierschutzkommission der Landeshauptstadt Kassel,
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The successful uptake and sustainability of rapid infectious disease and antimicrobial resistance point-of-care testing requires a complex »mix-and-match« implementation package.


From the document, the text suggests that the successful implementation of rapid infectious disease and antimicrobial resistance point-of-care testing requires a complex implementation package. This approach involves combining different elements to achieve the desired outcomes. The text references a study published in the European Journal of Clinical Microbiology & Infectious Diseases, emphasizing the importance of a systematic and adaptable strategy for improving healthcare diagnostics and response strategies.


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ABSTRACTS

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Szardenings M. Stand Mini-project PsA PsO Sere-nevaluierung. Kompetenzplattform »Neue Therapien«, ImmuMed Cluster Meeting, October 8, 2019, Leipzig, Germany

Tárno A. *Publishing in high impact journals: advice and tips from Cytometry A.* Invited Lecture: Advances in High-Content Single Cell Analysis, Sino-US Workshop, July 6–11, 2019, Shanghai, China

Trädler T. *Business Development and BD Contractual Law.* KIC Europe Workshop am Fraunhofer IZI, August 27, 2019, Leipzig, Germany

Trädler T. *Fraunhofer IZI – Regenerative Medicine Strategies & Projects.* JSRM Annual Meeting 2019, March 21, 2019, Kobe, Japan

Trädler T. *Showcase 4: Fraunhofer IZI.* 3rd KDDF Global TechFair, February 20, 2019, Seoul, South Korea

Tretbar US. *Maßgeschneiderte mizellare Nano-Carrier als Transfektionssystem für mRNA zur Adressierung von Immunzellen.* Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD, October 28, 2019, Frankfurt am Main, Germany

Uhlig K. *Zellablösung mittels Temperatur für anspruchsvolle Zellkultivierung.* Analysieren, Kultivieren, Desinfizieren – Ein Anwenderblick auf neue Polymere und Oberflächen in der Biotechnologie, September 11, 2019, Potsdam, Germany

Valdez-Ferraz C. *DRS stimulation with DNA-templated multivalent arrangements of TRAIL-mimicking peptides.* DNA Mitteldeutschland, November 29, 2019, Leipzig, Germany


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BOOK ARTICLES


Sandetskaya N. Advances in the detection of pathogen in sepsis diagnostics. Endotoxin detection and control in pharma, limulus, and mammalian systems (2019), pages 787-806. doi: 10.1007/978-3-030-17148-3_21

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Vogel M, Tangermann P. Better treatment for diabetic foot ulcers. Fraunhofer Research News / October 1, 2019

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Arndt, Nina. Fluoreszenz-optische Charakterisierung einer zwitterionischen Antifouling Beschichtung. Technische Universität Berlin, Bachelor thesis

Banek, Angela. Influence of glyphosate and its formulations on intestinal epithelial cell lines and commensal bacteria in vitro. University of Mannheim, Bachelor thesis


Behm, Laura. Thermo-responsive Zellkultursubstrat für zeitlich-räumlich gesteuertes Auswachsen neuronaler Zellen. University of Potsdam, Doctoral thesis


Bräuer, Dennis. Site-specific incorporation of non-canonical amino acids into cation channels using a tyrosine-based orthogonal tRNA/trNA-synthetase pair in eukaryotic cell-free systems. Beuth University of Applied Sciences Berlin, Master thesis

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Didwischus, Nadine. Cognitive decline of spontaneously hypertensive mice correlates with hypertensive immunophenotype. Leipzig University, Doctoral thesis

Ettingshausen, Johanna. Screening of microalgae and cyanobacteria for UV-absorbing substances. Technische Universität Berlin, Bachelor thesis


Feist, Henriette Victoria. Reinigung, enzymkinetische Untersuchung und Co-Kristallisation der bakteriellen Urease aus Sporosarcina pasteurii im Komplex mit ausgewählten Inhibitoren. Martin Luther University Halle-Wittenberg, Master thesis

Flechner, Marie. Optimierung der Zellkulturbedingungen in 3D Kollagenmatrices eines Mikrobioreaktors zur Untersuchung von Paracetamol-induzierter Hepatotoxizität. Technische Universität Berlin, Master thesis

Gabriel, Franziska. A cultivation protocol for growing P19-derived neurons on micropatterned temperature-responsive surfaces for controlled neuronal network formation. Freie Universität Berlin, Bachelor thesis
Hillmer, Jasmine. **Validierung eines neuartigen Workflows zur Generierung von Leitstrukturen in der Wirkstoffforschung.** Martin Luther University Halle-Wittenberg, Bachelor thesis

Jansig, Edith. **Untersuchungen zur Eignung von Viromeren als neue Trägermaterialien für die Gentherapie entzündlicher Erkrankungen.** Leipzig University, Doctoral thesis

Kamischke, Julia. **Untersuchungen zur Stabilisierung des in-vivo-Phänotyps von Mikroglia in der Zellkultur.** Martin Luther University Halle-Wittenberg, Master thesis

Kitte, Reni. **Isolation and characterization of anti-microbial phytosubstances from Warburgia ugandensis in vitro.** HTW Berlin – University of Applied Sciences, Master thesis

Krüger, Karolin. **Einfluss von kommensalen Bakterien auf das Wachstum und die Toxinproduktion von Clostridium difficile.** University of Rostock, Master thesis

Kurt, Büsra. **Untersuchungen zur Detektion von zirkulärer RNA mittels onChip-PCR.** Beuth University of Applied Sciences Berlin, Bachelor thesis

Lenschow, Lukas. **Identification of peptide epitopes recognised by sera of patients with fish allergy – Identifizierung von Peptid-Epitopen, die durch Patienten-Seren mit Fischarter erkannt werden.** Universität zu Lübeck, Master thesis

Lerma Romera, Jorge Alberto. **Optimization and characterization of a human and murine anti-isoaspartate-Αβ-antibody.** Martin Luther University Halle-Wittenberg, Master thesis

Markshaunen, Angelina. **Stabilitätsuntersuchungen eines monoklonalen anti-CD4 Antikörpers mittels nanoDSF-Technologie.** Mittweida University of Applied Sciences, Bachelor thesis

Matiebe, Anne. **Etablierung von Methoden für die in-vitro-Charakterisierung der NK-92-Zelllinie nach einer Elektronenstrahl-basierten Inaktivierung.** Anhalt University of Applied Sciences, Master thesis

Nottebrock, Alessia. **Charakterisierung und Etablierung eines Modells der moderaten, chronischen Niereninsuffizienz (Chronic Kidney Disease, CKD) in Wistar-Ratten.** University of Applied Sciences Jena, Master thesis

Oelkers, Betty. **Die Rolle der SUMOylierung bei der ischämischen Stressantwort neuraler Zellen.** Leipzig University, Doctoral thesis

Popp, Georg. **Entwicklung eines effizienten echtzeitfähigen Bildfusions-Algorithmus.** Leipzig University of Applied Sciences (HTWK Leipzig), Master thesis


Reichelt, Hendrik. **Etablierung eines Immunassays für die Quantifizierung von Transcobalamin als Basis für die Entwicklung eines Lateral-Flow-Tests für aktives B12.** Mittweida University of Applied Sciences, Master thesis

Sabrowski, Wiebke. **Generation and characterization of DNA aptamers against small molecules using Capture-SELEX.** Freie Universität Berlin, Master thesis

Santa-ardhampreech, Suttinee. **Studies on hazelnut epitopes of antibodies in sera from allergy patients and immunized rabbits.** Martin Luther University Halle-Wittenberg, Master thesis

Schaller, Julia. **Charakterisierung des Zellverhaltens auf thermoressiven Polymeroberflächen.** Humboldt-Universität zu Berlin, Master thesis

Schilling, Stephan. **Untersuchungen zur Rolle N-terminaler Peptidmodifikationen bei dementiellen Erkrankungen sowie daraus folgende Ansätze zur Unterdrückung pathophysiologischer Prozesse.** Martin Luther University Halle-Wittenberg, Habilitation

Schloßhauer, Jeffrey. **Qualifying a mutually orthogonal pyrrollysyl-tRNA synthetase-trNA(Pyl) pair for fluorescent labeling of anion channels in eukaryotic cell-free systems.** Freie Universität Berlin, Master thesis

Schöne, Lisa Marie. **Reducing phototoxicity using new live cell imaging devices.** Technische Universität Dresden, Master thesis
Seydel, Aleksandra. *Establishment and characterization of a mouse model of chronic Salmonella enterica infection as a proposed animal model for human inflammatory bowel disease.* Leipzig University, Doctoral thesis

Soyka, Nico. *Biochemische und molekularbiologische Charakterisierung von Mastitis-Erregern aus Milchproben.* University of Potsdam, Bachelor thesis

Teneng, Bertrand Tangu. *Silencing »Alu RNA« as a potential therapy for Age-related Macular Degeneration (AMD).* Martin Luther University Halle-Wittenberg, Master thesis

Vargas Rodriguez, Angela Maria. *Investigation of recombinant protein production in cytoplasm and periplasm using Vibrio natriegens.* Martin Luther University Halle-Wittenberg, Master thesis


Zemella, Anne. *Fluoreszenzmarkierung und Modifizierung von komplexen Proteinen in eukaryotischen zellfreien Systemen durch die Etablierung von orthogonalen tRNA/Aminoacyl-tRNA-Synthetase-Paaren.* University of Potsdam, Doctoral thesis
PRIZES

Award from the HTW Berlin – University of Applied Sciences for one of the best degrees in 2019 awarded to Reni Kitte at the end of the master study

Best Poster Award des 2nd European Biosensor Symposium 2019 für Christian Warmtm zum Thema “Novel RT-PCR based assay for the fast detection of circular RNAs (circRNA)”

Excellence award 2019 of the Fraunhofer-Gesellschaft awarded to PD Dr. Stephan Fricke on the topic “GvHD prevention”


Fraunhofer IZI Science Day poster prizes were awarded to Ioana Sonya Ciulean on the topic “Head and neck cancer therapy with CAR-NKs” / to Christin Möser on the topic “Oligovalent enhancement of biomolecules presented on DNA nanostructures” / to Michael Rade on the topic “Gene expression profiling during activation of human naïve T cells”

Fraunhofer IZI Science Day publication prizes were awarded to Dr. Jessica Freitag on the topic “Synthetic transient crosslinks program the mechanics of soft, biopolymer-based materials” / to Dr. Daniel Ramsbeck on the topic “Structure-guided design, synthesis, and characterization of next-generation meprin β inhibitors” / to Nadja Hilger on the topic “Incubation of Immune Cell Grafts With MAX.16H5 IgG1 Anti-Human CD4 Antibody Prolonged Survival After Hematopoietic Stem Cell Transplantation in a Mouse Model for Fms Like Tyrosine Kinase 3 Positive Acute Myeloid Leukemia”

Karl Schügerl Prize 2019 awarded by the Institute of Technical Chemistry of the Leibniz University Hannover to Julia Penk on the topic “Optimization of the upstream process and establishment of the downstream sequence for GMP-compliant biotechnological production of a humanized anti-CD4 IgG4 antibody”

PhD sponsorship of Leipzig University Medicine awarded to Phil Rademacher on the topic “Importance of extracellular vesicles in inflammatory processes”

Poster Award of the Aptamers 2019 – 6th International Symposium of the International Society on Aptamers (INSOAP) awarded to Wiebke Sabrowski on the topic “Generation of DNA aptamers against small molecules using Capture-SELEX”

Posterprize of the 15th Research Festival for Life Sciences of Leipzig University awarded to Dr. Markus Kreuz on the topic “Prognostic biomarkers in prostate carcinoma”

Promotion prize of the Faculty of Medicine of Leipzig University awarded to Dr. Alexandra Rockstroh on the topic “Development of methods for the specific, serological diagnosis of dengue and zika virus infections with modified envelope proteins”
PATENTS

The patent portfolio of the Fraunhofer IZI currently holds 50* patent families which are available for use in cooperation projects as well as for direct commercialization and licensing.

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FRAUNHOFER IZI HOLDS PATENT FAMILIES IN THE FOLLOWING FIELDS OF TECHNOLOGY

- Technologies for generating pluripotent stem cells
- Procedures for diagnosing infecting agents
- Procedures for diagnosing cancerous diseases
- New treatment procedures for cancer and other diseases
- New procedure for preventing graft-versus-host-disease (GvHD)
- Method for immobilizing cells on surfaces
- Procedure for diagnosing dyslexia
- Methods for ascertaining liver function and regeneration
- Procedure for diagnosing chronic lung diseases
- Mineral compounds for the prevention / treatment of kidney and bowel diseases
- Methods of treating neurological and neuropsychological diseases
- Substrate, cultivation facility and cultivation procedures for biological cells
- Electrochemical detection methods for binding reactions
- Cell-free protein synthesis procedure
- Procedure for manufacturing zinc fingers and concatemers
- Coimmobilization of several chemical species
- Procedure for manufacturing transparent films from cellulose dispersions and their use as multifunctional ligand carriers
- Device for measuring luminescence
- Procedure for manufacturing a leukocyte preparation
- Development of antimicrobial peptides
- Treating neurogenic immunodepression following brain injuries
- Technologies for generating pluripotent stem cells
- Biomarkers and diagnostic systems for application in human or veterinary medicine
- RNA species for therapeutic and / or diagnostic use
- Treatment approaches for cancer
- Procedures and devices for point-of-care diagnostics
- Drugs for the treatment of infectious as well as fibrotic and neurodegenerative diseases
- Procedure for immunomodulation and treatment of immunological diseases
- Surface modification
- Inactivating pathogens as part of vaccine production and novel vaccine candidates
- Methods for transferring nucleic acids into cells
- Epitopes from food relevant to the development of allergies
- Procedure for transplanting microbiomes
- Components of microscopical systems, especially from light sheet microscopy
- Methods for ascertaining liver function and regeneration
- Mineral compounds for the prevention / treatment of kidney and bowel diseases
- Dialysis procedures and novel components of dialysis systems
- Biomarkers and diagnostic procedures for dyslexia based thereon

* without Fraunhofer IZI-BB patents
FURTHERANCE
SPONSORS AND ADVISORY BOARD OF THE FRAUNHOFER IZI

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

SPONSORS

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

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

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

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THE FRAUNHOFER-GESELLSCHAFT

The Fraunhofer-Gesellschaft is the world’s leading applied research organization. With its focus on developing key technologies that are vital for the future and enabling the commercial exploitation of this work by business and industry, Fraunhofer plays a central role in the innovation process. Based in Germany, Fraunhofer is an innovator and catalyst for groundbreaking developments and a model of scientific excellence. By generating inspirational ideas and spearheading sustainable scientific and technological solutions, Fraunhofer provides science and industry with a vital base and helps shape society now and in the future.

At the Fraunhofer-Gesellschaft, interdisciplinary research teams work together with partners from industry and government in order to transform novel ideas into innovative technologies, to coordinate and realize key research projects with a systematic relevance, and to strengthen the German and the European economy with a commitment to creating value that is based on human values. International collaboration with outstanding research partners and companies from around the world brings Fraunhofer into direct contact with the key regions that drive scientific progress and economic development.

Founded in 1949, the Fraunhofer-Gesellschaft currently operates 74 institutes and research institutions. The majority of our 28,000 staff are qualified scientists and engineers, who work with an annual research budget of 2.8 billion euros. Of this sum, 2.3 billion euros is generated through contract research. Around 70 percent of Fraunhofer’s contract research revenue is derived from contracts with industry and publicly funded research projects. The remaining 30 percent comes from the German federal and state governments in the form of base funding. This enables the institutes to work on solutions to problems that are likely to become crucial for industry and society within the not-too-distant future.

Applied research also has a knock-on effect that is felt way beyond the direct benefits experienced by the customer: our institutes boost industry’s performance and efficiency, promote the acceptance of new technologies within society, and help train the future generation of scientists and engineers the economy so urgently requires.
Our highly motivated staff, working at the cutting edge of research, are the key factor in our success as a scientific organization. Fraunhofer offers researchers the opportunity for independent, creative and, at the same time, targeted work. We therefore provide our employees with the chance to develop the professional and personal skills that will enable them to take up positions of responsibility at Fraunhofer, at universities, in industry and within society. Students who work on projects at Fraunhofer Institutes have excellent career prospects in industry by virtue of the practical training they enjoy and the early experience they acquire of dealing with contract partners.

The Fraunhofer-Gesellschaft is a recognized non-profit organization that takes its name from Joseph von Fraunhofer (1787–1826), the illustrious Munich researcher, inventor and entrepreneur.

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BY CAR
A9 – Exit Leipzig-West: Take the B181 in the direction of the city center (“Zentrum”) and follow the B87 (Merseburger Straße, Lützner Str., Jahnallee). After passing the central station, turn right towards Augustusplatz (Leipzig Opera House). At Augustusplatz turn left and keep to the right, then follow Prager Straße. Turn right at Semmelweisstraße, follow the road and then turn left onto Zwickauer Straße. Follow this road until you turn left into Perlickstraße.

A14 – Exit Leipzig-Mitte: Take the B2 (via Maximilianallee) in the direction of the city center (“Zentrum”) and follow the B2 (via Gerichtsweg). Turn left onto Prager Straße (B2) in the direction of “Alte Messe”, then turn right onto “Alte Messe”. Turn right at Semmelweisstraße, follow the road and then turn left onto Zwickauer Straße. Follow this road until you turn left into Perlickstraße.

A38 – Exit Leipzig-Süd: Take the B2 in the direction of the city center (“Zentrum”) and turn off at exit “Richard-Lehmann-Straße”. Follow Richard-Lehmann-Straße and turn off before the BMW car dealership onto Zwickauer Straße in
the direction of “Alte Messe”, then turn right onto Perlickstraße.

The car park is accessible from Perlickstraße. You will find visitors’ parking right in front of the façade of the institute.

BY TRAIN AND PUBLIC TRANSPORT

Take the train to Leipzig Hauptbahnhof central station, and then continue with tram line 16 towards Lößnig. Get off at the stop “An den Tierkliniken”, directly opposite the institute. The closest overground train (“S-Bahn”) station is “Leipzig MDR” and all overground trains stop there (10–15 minute walk to the institute).

FROM THE AIRPORT

With the overground train (“S-Bahn”) towards Leipzig Central Station, then follow the directions given under “Train and Public Transport”.
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