Fraunhofer

IZI

FRAUNHOFER INSTITUTE FOR CELL THERAPY AND IMMUNOLOGY IZI

ANNUAL REPORT 2019

This is the abridged version of the Fraunhofer IZI Annual Report 2019.

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

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

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

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HIGHLIGHTS AND EVENTS 2019

THE FRAUNHOFER IZI IN PUBLIC

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.

JANUARY 24, 2019: NEW YEAR'S RECEPTION

Together with the Fraunhofer Center for International Management and Knowledge Economy IMW and biosaxony e. V., Fraunhofer IZI invited guests to the New Year's reception. 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.

FEBRUARY 2019: POSITIVE EVALUATION OF THE ROSTOCK DEPARTMENT

Rostock-based project group Extracorporeal Immunomodulation has been developing new diagnosis and treatment methods in the field of extracorporeal organ replacement systems since 2011. An external expert committee positively assessed the off-site department in February 2019 and recommended its permanent integration in the organization – a recommendation which was followed by the Fraunhofer-Gesellschaft's Executive Board and the Bund-Länder Commission (BLK). Since January 1, 2020, the off-site department has been included in the Fraunhofer-Gesellschaft's regular 90:10 funding, thus safeguarding its future.

MARCH 28, 2019: GIRLS' DAY AND BOYS' DAY AT FRAUNHOFER IZI

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. The initiative saw eleven schoolgirls and ten schoolboys spend the day taking in the work of a biomedical research institute. 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.

APRIL 9, 2019: SCIENCE CINEMA "CLUB DER ROTEN BÄNDER – WIE ALLES BEGANN"

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 film looks at the origins of the Club der roten Bänder, or "Club of red bracelets", a German comedy-drama

1 *New Year's Reception 2019.*

2 *Boys'Day 2019 at Fraunhofer IZI.*

1

2

TV series that follows a group of teenagers living together as patients in a hospital's pediatric ward. The podium discussion held after the showing was centered around questions on the current state of cancer research and cancer medicine.

JUNE 11, 2019: SAXONY'S MINISTER PRESIDENT MICHAEL KRETSCHMER VISITS FRAUNHOFER IZI

At an on-site visit, Professor Ulrike Köhl, Director of Fraunhofer IZI, and Heinrich Moisa, Managing Director of Novartis Oncology in Germany, brought Saxony's Minister President Michael Kretschmer up to date 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.

SEPTEMBER 16 AND 17, 2019: DG-GT THEME DAY "CAR-T CELLS AND BEYOND"

Around 200 distinguished international experts and junior researchers from the field of cell and gene therapy discussed the latest developments in immuno-oncology as part of the DG-GT theme day "CAR-T cells and beyond" at Fraunhofer IZI. The spotlight was placed on current preclinical and clinical developments, trends in the manufacture of gene transfer vectors, as well as ethical and regulatory aspects associated with the novel immunotherapies.

OCTOBER 7, 2019: 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. In Germany, more than fifteen hospitals (effective September 2019) have been certified to carry out this treatment. Novartis has worked closely together with Fraunhofer IZI to establish a complex manufacturing process for CAR-T cells.

NOVEMBER 8, 2019: FRAUNHOFER MEOS SHOWCASES ITS WORK AT THE LONG NIGHT OF THE SCIENCES IN ERFURT

The Fraunhofer project center Microelectronic and Optical Systems for Biomedicine MEOS took part in the Long Night of the Sciences in Erfurt for the first time, showcasing its work to interested guests. The project center brings together Fraunhofer IZI with the Fraunhofer Institutes for Photonic Microsystems IPMS and for Applied Optics and Precision Engineering IOF.

3

DECEMBER 2, 2019: IMSAVAR KICK-OFF MEETING

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. 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.

LOOKING TO 2020

LION
LEIPZIG
IMMUNE ONCOLOGY
CONFERENCE
2020

November 10–11 2020 | Leipzig, Germany
Leipzig Immune ONcology (LION) Conference
www.lion-conference.com

Further information on the events can be found in the full version of the annual report on pages 5–8. https://s.fhg.de/KJ2

1 *Saxony´s minister president Michael Kretschmer (2nd from left) visits Fraunhofer IZI.*
2 *DG-GT Theme Day "CAR-T cells and beyond"*
3 *Kick-off meeting for EU project imSAVAR.*

STRUCTURES AND FIGURES 2019

PORTRAIT OF THE INSTITUTE

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

- Diagnostics
- Drugs & biologicals
- Cell and gene therapy

COMPETENCIES

- Bioanalytics
- Biomarkers
- Therapeutic molecules
- Cell techniques

ORGANIZATION

MAY 1, 2020

DIRECTOR

Prof. Dr. 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

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

- Preclinical Models, Sina Riemschneider
- Protein Biomarker, Prof. Dr. Stefan Kalkhof
- Cell Line Development, Dr. Elke Ueberham
- Manufacturing Biopharmaceuticals, Dr. Lukasz Hudak
- Quality Control Biopharmaceuticals, Dr. Jens Knauer
- Veterinary Pathology, Dr. Anke Hoffmann

DEPARTMENT OF IMMUNOLOGY

PD Dr. Sebastian Ulbert

- Vaccine Technologies, PD Dr. Sebastian Ulbert
- Immune Tolerance, PD Dr. Stephan Fricke
- Image Analysis of Cell Function, Prof. Dr. Ulf-Dietrich Braumann
- Preclinical Validation, Dr. Thomas Grunwald
- Ligand Development, Dr. Michael Szardenings
- Antimicrobial Agents, Dr. Andreas Schubert
- Biological Material Analytics (Fraunhofer IKTS ATTRACT-Group), Dr. Juliane Spohn

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
- MicroDiagnostics, Dr. Dirk Kuhlmeier
- DNA Nanodevices, Dr. David M. Smith
- CardiOmics, Prof. Dr. Dr. Dr. Andreas Oberbach
- Next-Generation Diagnostics, Dr. Conny Blumert
- Bioinformatics, Dr. Kristin Reiche

HEADQUARTER LEIPZIG

BRANCH BIOANALYTICS AND BIOPROCESSES

Dr. Eva Ehrentreich-Förster (temp.)

MARKETING & COMMUNICATION

Dr. Katharina Kasack

ADMINISTRATION

Katja Okulla

DEPARTMENT OF EXTRACORPOREAL IMMUNO-MODULATION

Prof. Dr. Steffen Mitzner

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 Schulze

DEPARTMENT OF BIOSYSTEMS INTEGRATION AND PROCESS AUTOMATION

PD Dr. Ralph Hölzel (temp.)

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

DEPARTMENT OF MOLECULAR AND CELLULAR BIOANALYTICS

Dr. Eva Ehrentreich-Förster

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

DEPARTMENT OF CELL-FREE AND CELL-BASED BIOPRODUCTION

Dr. Stefan Kubick

- Cell-free Protein Synthesis, Dr. Stefan Kubick
- Eukaryotic Lysates, Doreen Wüstenhagen
- Functional Nucleic Acids – Aptamers, Dr. Marcus Menger
- Extremophile Research and Biobank CCCryo, Dr. Thomas Leya

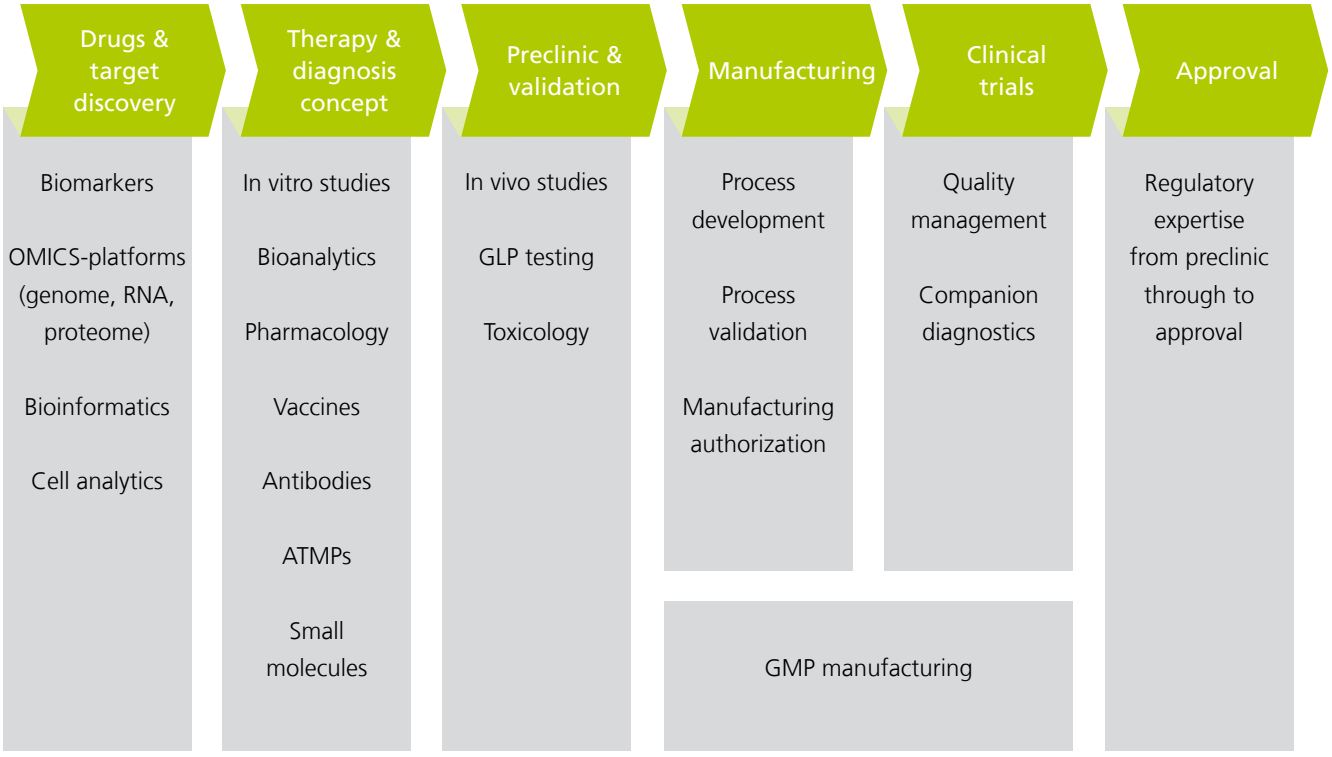
ROSTOCK | HALLE (SAALE) | POTSDAM-GOLM

BUSINESS UNITS

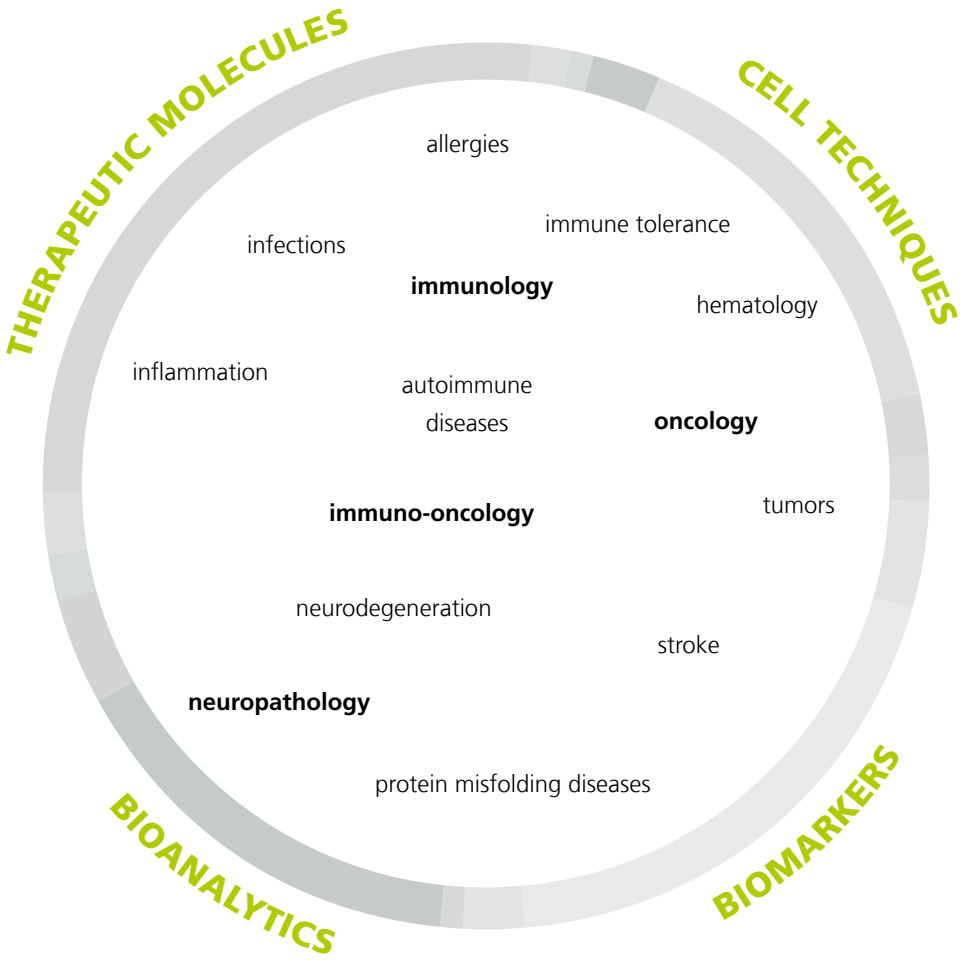
CELL AND GENE THERAPY

DRUGS & BIOLOGICALS

DIAGNOSTICS



COMPETENCIES AND INDICATIONS



KEY INSTITUTE FIGURES 2019

AS AT DECEMBER 31, 2019

PROJECT REVENUE

by funding agency

50,6 %
Industry
(TEUR 17 412)

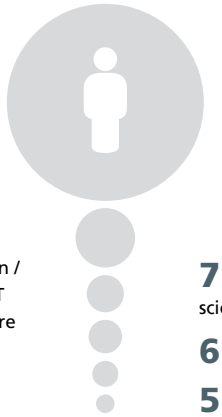
26,6 %
German national and regional government
(TEUR 9 166)

21,9 %
Other (TEUR 7 520)

0,9 %
EU (TEUR 304)

EMPLOYEES

Workforce composition



57 % Scientists incl. visiting scientists

15 % Technical assistants and laboratory technicians

10 % Administration / executive departments / IT and technical infrastructure

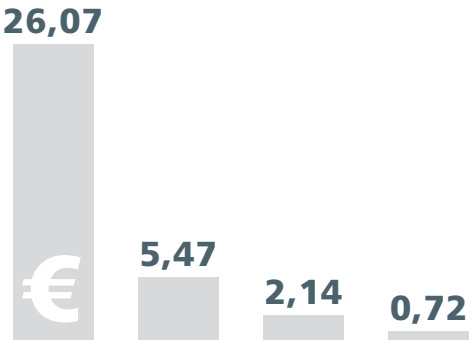
7 % Student / scientific assistants

6 % PhD students

5 % Interns / degree candidates / Bachelor students / Master students / trainees

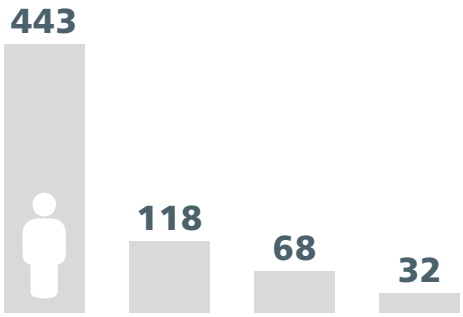
€ 34,4 MIO PROJECT REVENUE

by location in € mio



661 EMPLOYEES

by location



SCIENTIFIC PRESENCE AND NETWORK 2019

86 Conventions and conferences

184 Industry partners
174 Research partners

201 Abstracts
79 Publications
6 Book articles
1 Book

53 Teaching activities

1 Habilitation
6 Doctorates
1 Diploma theses
27 Master theses
12 Bachelor theses

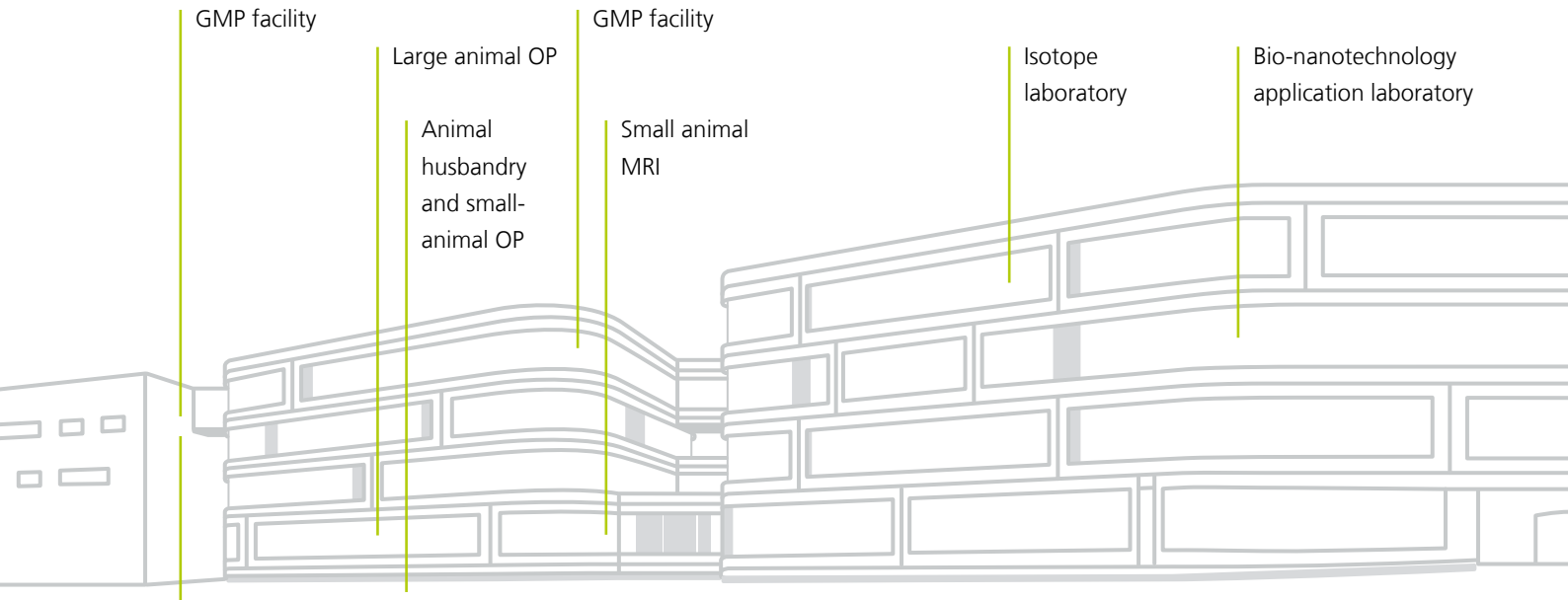
50 Patent families
174 Patents and patent applications

47 Evaluator activities

117 Association memberships in various expert associations

Detailed information on key figures and publications can be found in the full version of the annual report on pages 111–149.
https://s.fhg.de/CF8

RESEARCH INFRASTRUCTURE AT THE LEIPZIG SITE



FIRST EXTENSION BUILDING

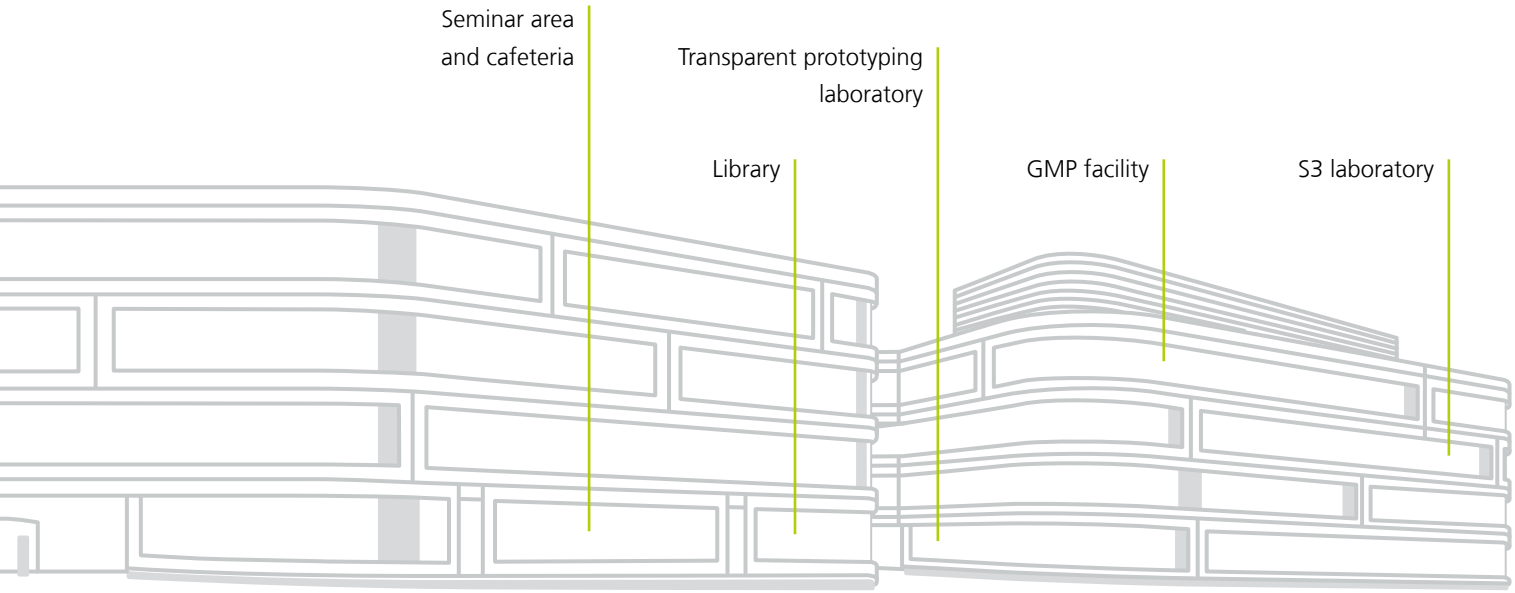
Start-up operations: 2012
Usable area: 1 568 m²
Lab space: 470 m²
Offices: 142 m²
Clean rooms: 410 m²

MAIN BUILDING

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

RENTAL AREA AT BIO CITY LEIPZIG

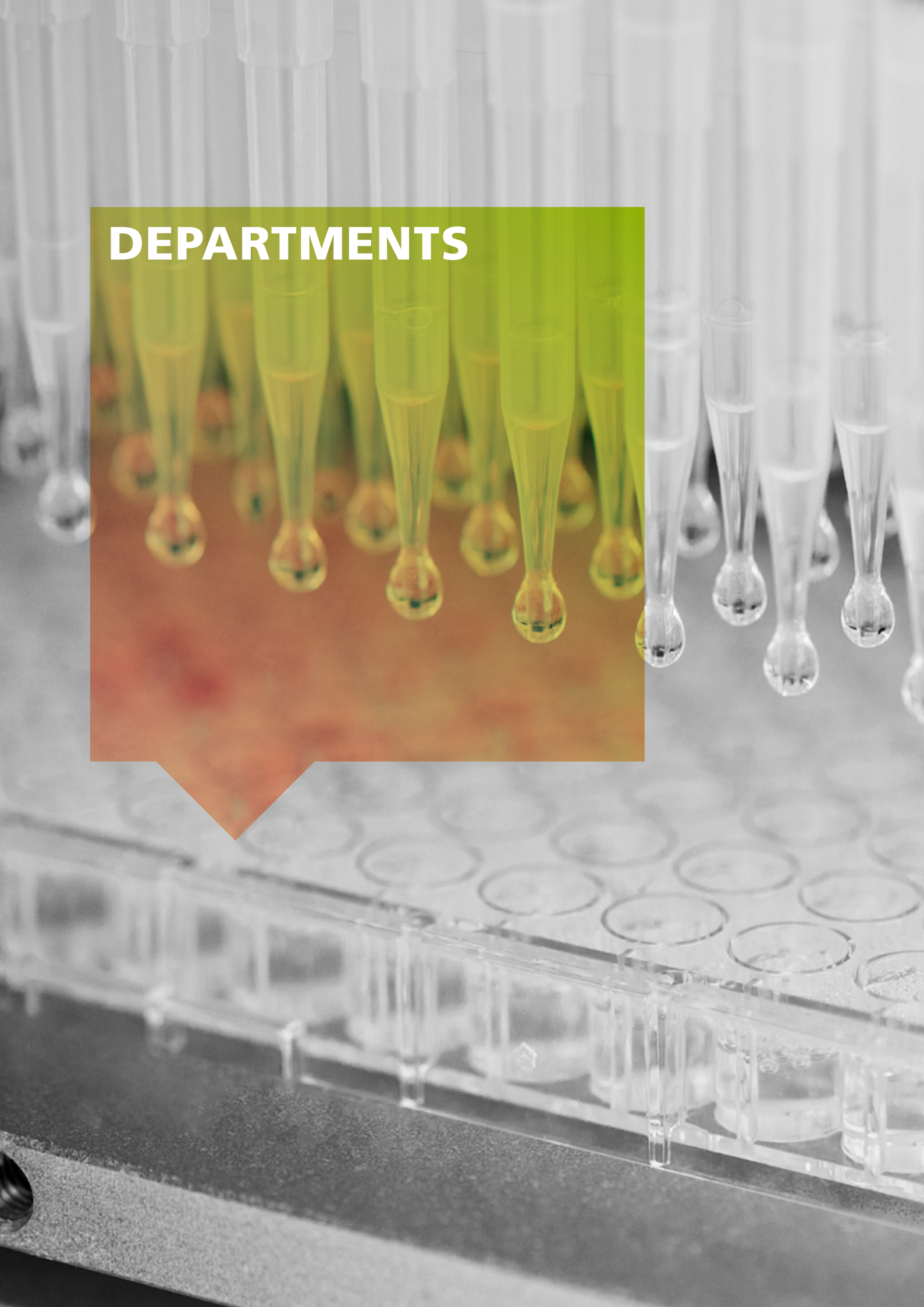
Start-up operations: 2006
Clean rooms: 334 m²



SECOND EXTENSION BUILDING

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

DEPARTMENTS



GMP CELL AND GENE THERAPY

THE MAIN DEPARTMENT AT A GLANCE

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.

CONTACT

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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 extracted in the clinic by leukapheresis before being genetically reprogrammed in vitro in such a way that they can use a chimeric antigen receptor to recognize cancer cells with a special antigen on their surface and initiate their destruction. This immunotherapeutic agent was manufactured for use in clinical trials on behalf of Novartis AG and approved by the European Commission for two indications in summer 2018.

ROR1 CAR-T POC INITIATIVE: CAR-T CELLS FOR THE TREATMENT OF BREAST AND LUNG CANCER

Following the clinical success of CAR-T cell therapy in treating hematological cancers, intensive research is now under way to expand the technology to also treat other types of cancer. CAR-T cells designed to target the surface molecule ROR1 are to be used to address solid tumors such as breast and lung cancer. As part of the project, a chimeric antigen receptor (CAR) developed at the University of Würzburg and the cell therapy based on this receptor are undergoing preclinical testing with an eye to efficacy and safety. Appropriate manufacturing and quality assurance processes are also being developed and adjusted at Fraunhofer IZI. The project has been granted funding under the proof-of-concept initiative launched by Fraunhofer, Helmholtz and Deutsche Hochschulmedizin.

Further information on the department and its projects can be found in the full version of the annual report on pages 18–21.
https://s.fhg.de/Pd8

GMP PROCESS DEVELOPMENT

THE DEPARTMENT AT A GLANCE

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.

CONTACT

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PROJECT EXAMPLE

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

Graft versus host disease (GvHD) is the main complication that occurs following hematopoietic stem cell transplantation. The transplant's immune response to the host can prove fatal or result in serious long-term damage with a lifelong need for treatment. 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.

Further information on the department and its projects can be found in the full version of the annual report on pages 22–24.
https://s.fhg.de/xza

THERAPY VALIDATION

THE DEPARTMENT AT A GLANCE

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.

UNITS

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

CONTACT

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joerg.lehmann@
izi.fraunhofer.de

PROJECT EXAMPLES

CONDUCT OF GLP TOXICITY STUDIES TO APPLY FOR TEST CATEGORY 2

The Department of Therapy Validation has been GLP certified since 2009 and is recognized as a test facility for conducting non-clinical drug trials in test category 9. Here the focus is on the non-clinical efficacy and safety testing of drug candidates such as advanced therapy medicinal products (ATMPs) and medical devices. An application is now being made for test category 2 based on a study that looks at the systemic toxicity of a therapeutic hepatitis B vaccine. This test category assesses the potential toxicity of new drug candidates and medical devices in human subjects. The project is funded under the proof-of-concept initiative launched by Fraunhofer, Helmholtz and Deutsche Hochschulmedizin.

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

Investigation of the aryl hydrocarbon receptor (AhR) as a new therapeutic target for strategies aimed at treating chronic inflammatory bowel diseases (IBD). A highly diagnostic pharmacophore model is to be developed based on the structure of the AhR, which will identify suitable ligands using structure- and ligand-based methods. These ligands will then be developed further as candidates to be used in future IBD treatment.

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

Bone tissue generally demonstrates a good regenerative capacity; this can, however, become severely limited in patients with type 2 diabetes. Finding the right treatment in the case of a fracture requires the use of diagnostic methods for assessing regeneration potential. This project aims to identify suitable biomarkers that can be used to support therapeutic decision-making processes. Moreover, patient-specific scaffold constructions are to be developed that will assist the otherwise prolonged healing of bone fractures. This will involve the integration of molecular and biomechanical models in a systems medicine platform.

Further information on the department and its projects can be found in the full version of the annual report on pages 25–32.
https://s.fhg.de/5yP

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.

UNITS

- Vaccine Technologies, PD Dr. Sebastian Ulbert
- Immune Tolerance, PD Dr. Stephan Fricke
- Image Analysis of Cell Function, Prof. Dr. Ulf-Dietrich Braumann
- Preclinical Validation, Dr. Thomas Grunwald
- Ligand Development, Dr. Michael Szardenings
- Antimicrobial Agents, Dr. Andreas Schubert
- Biological Material Analytics, Dr. Juliane Spohn

PROJECT EXAMPLES

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

The Vaccine Technologies Unit has developed a new manufacturing process for inactivated vaccines based on low-energetic electron irradiation.

DEVELOPMENT OF BIODEGRADABLE PESTICIDES BASED ON PLANT EXTRACTS WITH AN ANTIMICROBIAL EFFECT

The Antimicrobial Agents Unit is developing innovative, plant-based fungicide alternatives.

CONTACT

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PREVENTING ADVERSE IMMUNOLOGICAL COMPLICATIONS WHILE RETAINING ANTI-TUMOR EFFECT FOLLOWING STEM CELL TRANSPLANTATION INVOLVING ANTI-HUMAN CD4 ANTIBODIES

The main complication following allogeneic hematopoietic stem cell transplantation is acute graft versus host disease (aGvHD). An antibody-based treatment has been developed in the Immune Tolerance Unit that is expected to lessen or prevent this life-threatening immune reaction.

IMMUNOME MAPPING FOR PEPTIDE-BASED IMMUNODIAGNOSTICS

The Ligand Development Unit has designed a new way of identifying antibody binding sites (epitopes) with greater precision, also directly from patient serums. The method is being applied, among other things, in a project identifying food allergies.

EFFICACY TESTING OF A NOVEL HELICASE-PRIMASE-BASED THERAPY AGAINST THE HUMAN HERPES SIMPLEX VIRUS (HSV)

A therapy study is being conducted by the Preclinical Validation Unit to investigate a helicase-primase-based drug for treating herpes simplex virus infections in the mouse model.

VACCINATING AGAINST ASTHMA?

The Preclinical Validation Unit is investigating whether a vaccination against RSV is able to prevent repeated infections and, in turn, the development of asthma.

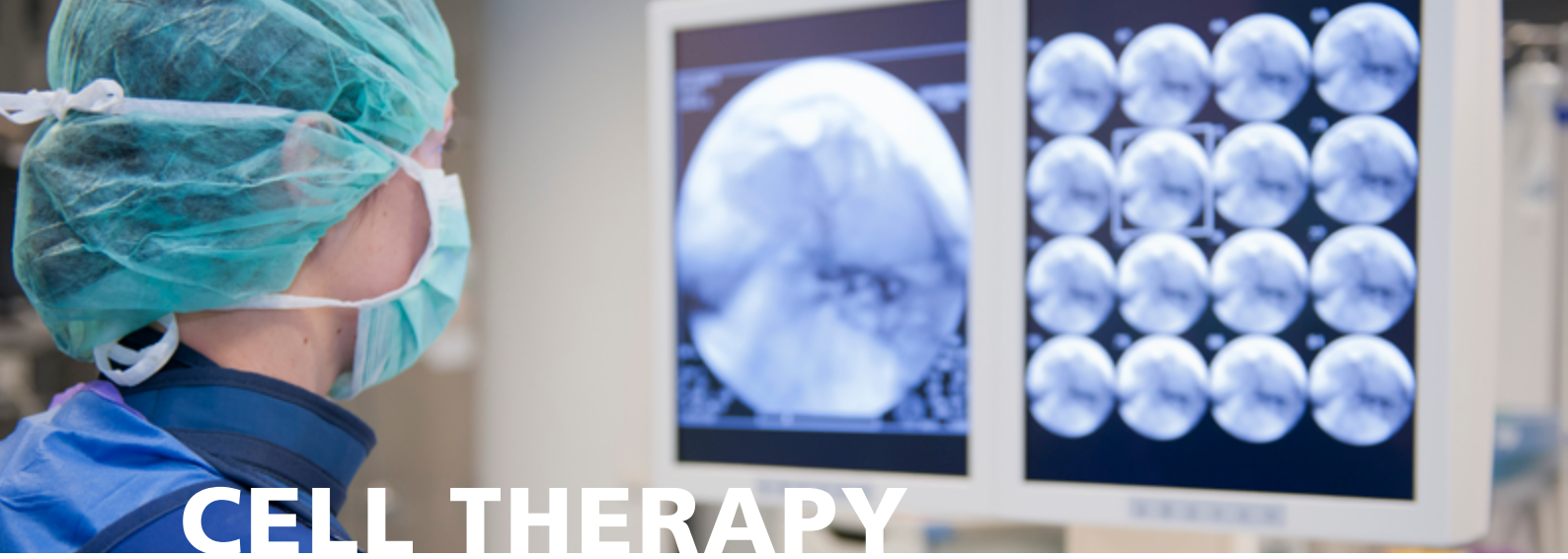
THERAVISION

Platform technology for the development, production and testing of oncolytic herpes simplex viruses in order to treat lung cancer.

RSV PROTECT

The respiratory syncytial virus (RSV) is largely harmless in healthy adults, however it poses a serious risk to the lives of babies, the elderly or patients with weakened immune systems. This project aims to develop strategies for protecting against RSV infections.

Further information on the department and its projects can be found in the full version of the annual report on pages 33–46.
https://s.fhg.de/wch



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.

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- Clinic-oriented Therapy Assessment, Dr. Antje Dreyer
- Branch Lab Translational Cell Therapy, Dr. Stephan Klöß

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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, NK cells combined with chimeric antigen receptors (CARs) are manufactured to specifically target various surface structures on solid tumors, i.e. squamous cell carcinoma, before being tested with an eye to efficacy.

EVALUATION OF A NEUROPROTECTIVE COCKTAIL IN ACUTE TRANSIENT STROKE IN THE SHEEP (SAVEBRAIN)

This project saw the testing of a novel therapy that draws on a combination of three substances to inhibit two neurotoxic mechanisms while at the same time activating a neuroprotective mechanism.

Further information on the department and its projects can be found in the full version of the annual report on pages 47–52.
https://s.fhg.de/d74

DIAGNOSTICS

THE DEPARTMENT AT A GLANCE

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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- Inflammation Models and Immunodiagnostics, Dr. Franziska Lange
- MicroDiagnostics, Dr. Dirk Kuhlmeier
- DNA Nanodevices, Dr. David M. Smith
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PROJECT EXAMPLES

CAR-NK CELL THERAPY FOR THE TREATMENT OF PERITONEAL METASTASES

Ovarian cancer is an aggressive form of cancer with a mortality rate of around 70 per cent. As its symptoms are non-specific and emerge at a very late stage, it is extremely difficult and rare to diagnose the disease early on. By the time the disease is diagnosed, the entire peritoneum has often already been affected by metastases. This project will test novel NK cell therapeutics with different CARs in a mouse model for peritoneal metastases.

DIAGNOSING DIFFERENT DISEASES IN EXHALED AIR USING ION-MOBILITY SPECTROMETRY

Diagnosing diseases should be quick, straightforward, affordable, and possible at the point of care, without the need for highly qualified laboratory staff and without exposing the patient to additional stress. In order to satisfy this need, a diagnostic procedure is to be developed that draws on exhaled air.

GLYCO3DISPLAY – SCREENING OF DNA-POLYSACCHARIDE CONSTRUCTS AS ANTI-PATHOGENIC SUBSTANCES

A large number of glycans (complex sugars) can be found on the surface of human cells. Pathogenic bacteria or viruses use these molecules to identify, bind and infect host cells. The Glyco3Display project will lay the foundations for developing diagnostic and therapeutic methods based on glycan-DNA conjugates.

Further information on the department and its projects can be found in the full version of the annual report on pages 53–60.
https://s.fhg.de/E5i

EXTRACORPOREAL IMMUNOMODULATION

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.

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PROJECT EXAMPLES

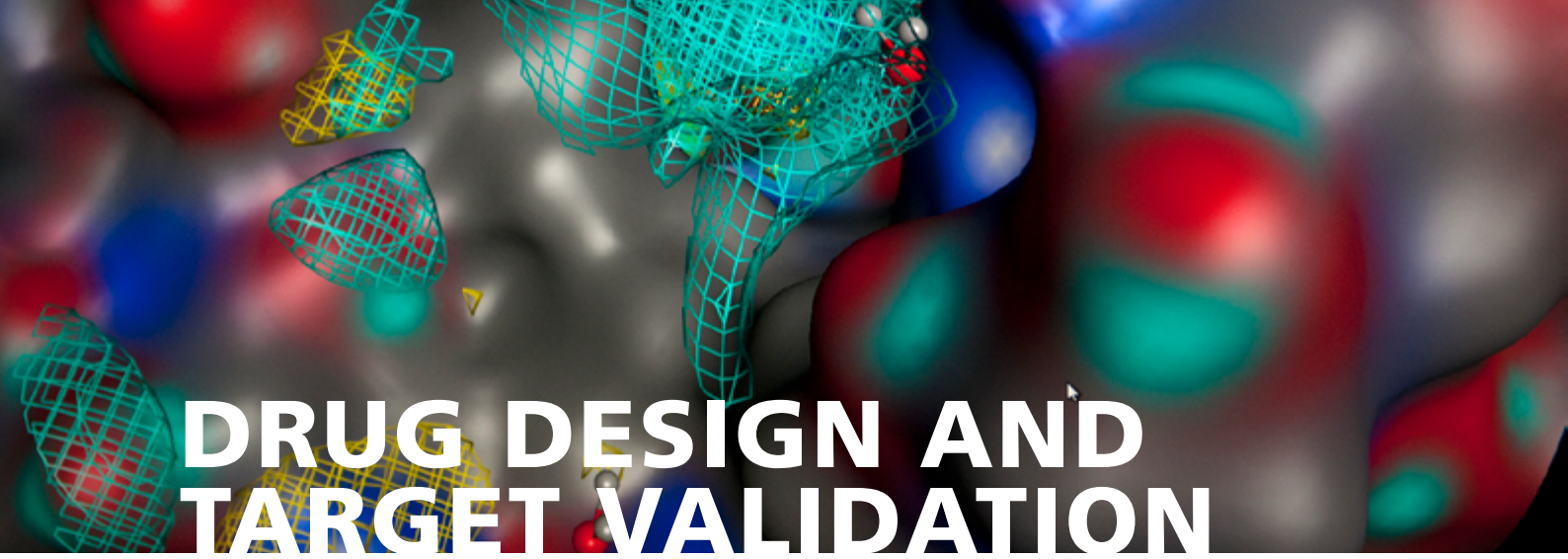
EX-SITU ORGAN PERFUSION

The availability of suitable donor organs for patients with organ failure has long posed a huge medical problem. Besides the general lack of organ donations, the number of transplantable organs is reduced further due to issues such as a lack of blood or oxygen supply to the organ during transportation from the donor to the recipient. By using an organ perfusion platform, new approaches are to be investigated that could enable the use of functionally impaired livers.

CRYOREGENERATION OF DIALYSIS WATER

Patients whose bodies have a weakened detoxification function due to a late-stage chronic kidney disease regularly need to have dialysis. Due to the frequent and time-intensive outpatient treatment, this procedure, which is essential for the patient's survival, is associated with enormous limitations in terms of quality of life and mobility. This is why the EXIM off-site unit is working on a way to make dialysis mobile.

Further information on the department and its projects can be found in the full version of the annual report on pages 61–64.
https://s.fhg.de/Vu5



DRUG DESIGN AND TARGET VALIDATION

THE DEPARTMENT AT A GLANCE

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.

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PROJECT EXAMPLES

ANTIBODIES FOR TREATING NEURODEGENERATIVE DISEASES

A number of neurodegenerative diseases are primarily caused by the depositing of defective proteins The Protein and Drug Biochemistry Unit is developing therapeutic antibodies that prompt the immune system to break down these protein aggregates, which is expected to result in a curative therapy.

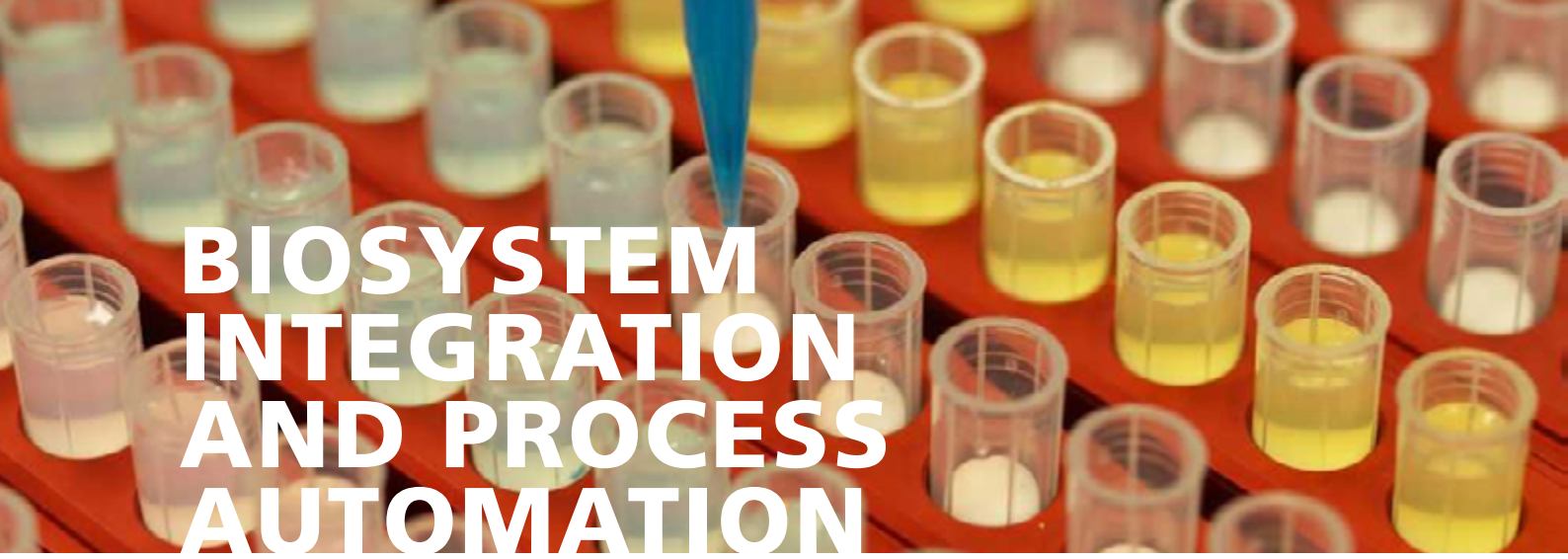
DETERMINING THE PHARMACOKINETIC PARAMETERS OF SMALL MOLECULES

A vital part of developing new drugs is characterizing them in terms of liberation, absorption, dispersion, metabolism and excretion (L-ADME parameter) in the animal model. This is intended, in particular, to provide information on the overall exposure of the organism, bioavailability following application and the half-life period of the active agent in the circulation. To assist with this, a catheter-based test procedure was established in the Molecular Biotechnology Unit to determine pharmacokinetic properties of small molecules in rats. The procedure is being used in the development of new drugs, for instance to treat neurodegenerative and inflammatory diseases.

BROADENING THE CHEMICAL SPACE OF METAL BINDING GROUPS

By drawing on computational chemistry procedures, the Drug Design and Analytical Chemistry Unit is supporting the development of new drugs whose target structures are metal ions in the catalytic center of enzymes. The procedure helps to identify specially tailored molecules which will then form the basis of manufacturing drugs with as specific an effect as possible.

Further information on the department and its projects can be found in the full version of the annual report on pages 65–71.
https://s.fhg.de/J4p



BIOSYSTEM INTEGRATION AND PROCESS AUTOMATION

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.

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- Biomimetic Functional Materials, Dr. Nenad Gajovic-Eichelmann
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PROJECT EXAMPLE

NEW RAPID ANTIBIOTICS TEST: BETTER TREATMENT FOR DIABETIC FOOT ULCERS

Patients with type 2 diabetes often suffer from open and infected wounds affecting the limbs, which have to be treated using antibiotics. Targeted and effective treatment thus requires the responsible pathogens to be identified as quickly as possible. A rapid test has therefore been developed which should enable the right antibiotics to be selected from the very start.

Further information on the department and its projects can be found in the full version of the annual report on pages 72–76.
https://s.fhg.de/rs8

MOLECULAR AND CELLULAR BIOANALYTICS

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.

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- Molecular Bio Engineering, Dr. Markus von Nickisch-Rosenegk
- Microsystems for In Vitro Cell Models, Dr. Katja Uhlig
- Microfluidic Cell Processing and Cell Analytics, Dr. Michael Kirschbaum

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PROJECT EXAMPLES

DEVELOPMENT OF A PHYSIOLOGICALLY RELEVANT TEST SYSTEM FOR THE IN-VITRO DETECTION OF HEPATOTOXICITY IN HIGH THROUGHPUT (HEPATOTOX)

The HepatoTox project will see the continued development of an organ-on-chip system with an eye to increased throughput and the use of relevant cell models. As well as the application of physiologically relevant cell models, reference substances will be used in the project to validate the organ-on-chip system, enabling an evaluation of the measuring system's relevance and efficiency. The aim here is to reduce the need for animal experiments in the future, which are used to test the hepatotoxicity of active ingredients.

BIODETECTOR – INTEGRATED DETECTION SYSTEM FOR BIOLOGICAL CONTAMINATION IN FUEL

The biological contamination of fuel is an important topic wherever large quantities of fuel are required or where they are stored for a long period of time (e.g. in the fields of transportation and agriculture). This project aims to develop an integrated detection system for the DNA-based verification of biological contamination in fuel that requires minimal user effort.

Further information on the department and its projects can be found in the full version of the annual report on pages 77–83.
https://s.fhg.de/cu9

CELL-FREE AND CELL-BASED BIOPRODUCTION

THE DEPARTMENT AT A GLANCE

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.

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- Cell-free Protein Synthesis, Dr. Stefan Kubick
- Eukaryotic Lysates, Doreen Wüstenhagen
- Functional Nucleic Acids – Aptamers, Dr. Marcus Menger
- Extremophile Research & Biobank CCCryo, Dr. Thomas Leya

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PROJECT EXAMPLE

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

The aim of this project is to carry out research into a novel 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.

Further information on the department and its projects can be found in the full version of the annual report on pages 84–88.
https://s.fhg.de/Zr3

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.

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GMP MANUFACTURING

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

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

BIOPHARMACEUTICALS

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

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

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).

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

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

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

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CENTER FOR EXPERIMENTAL MEDICINE

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

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

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

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

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

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

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

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

EQUIPMENT AND SERVICES:

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

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

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

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

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

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RIBOLUTION BIOMARKER CENTER

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.

CONTACT

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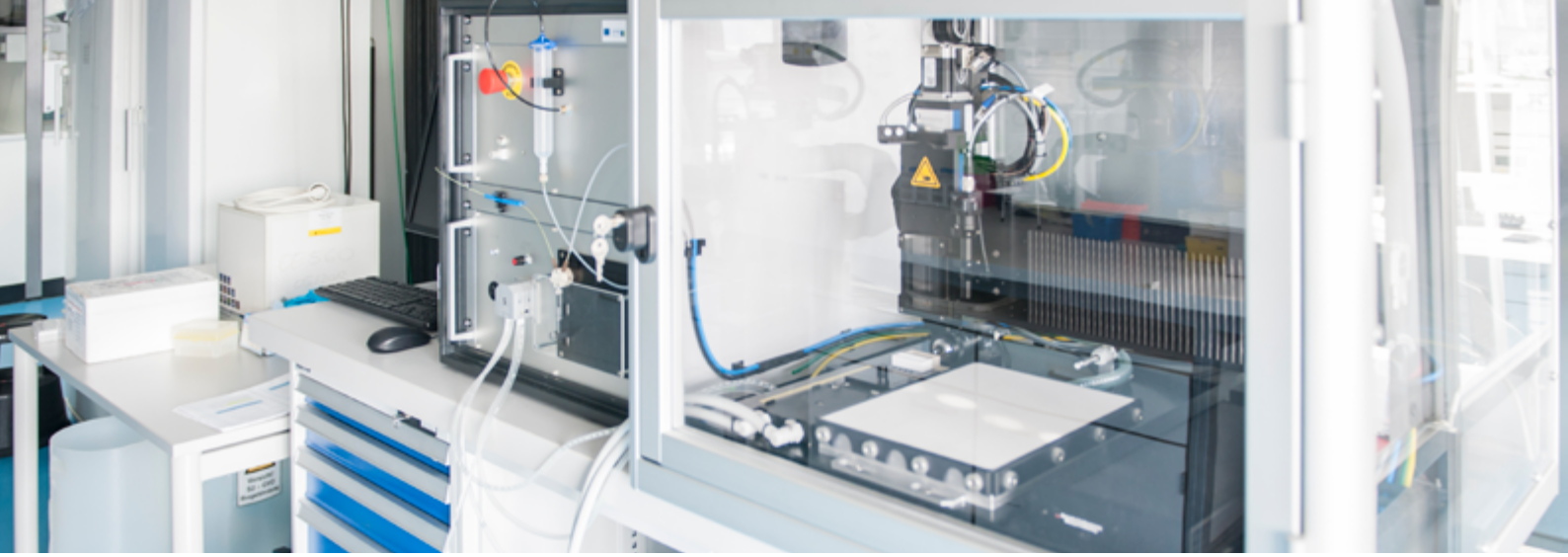

BIO-NANOTECHNOLOGY APPLICATION LABORATORY (BNAL)

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 neuro-degenerative 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 highenergy 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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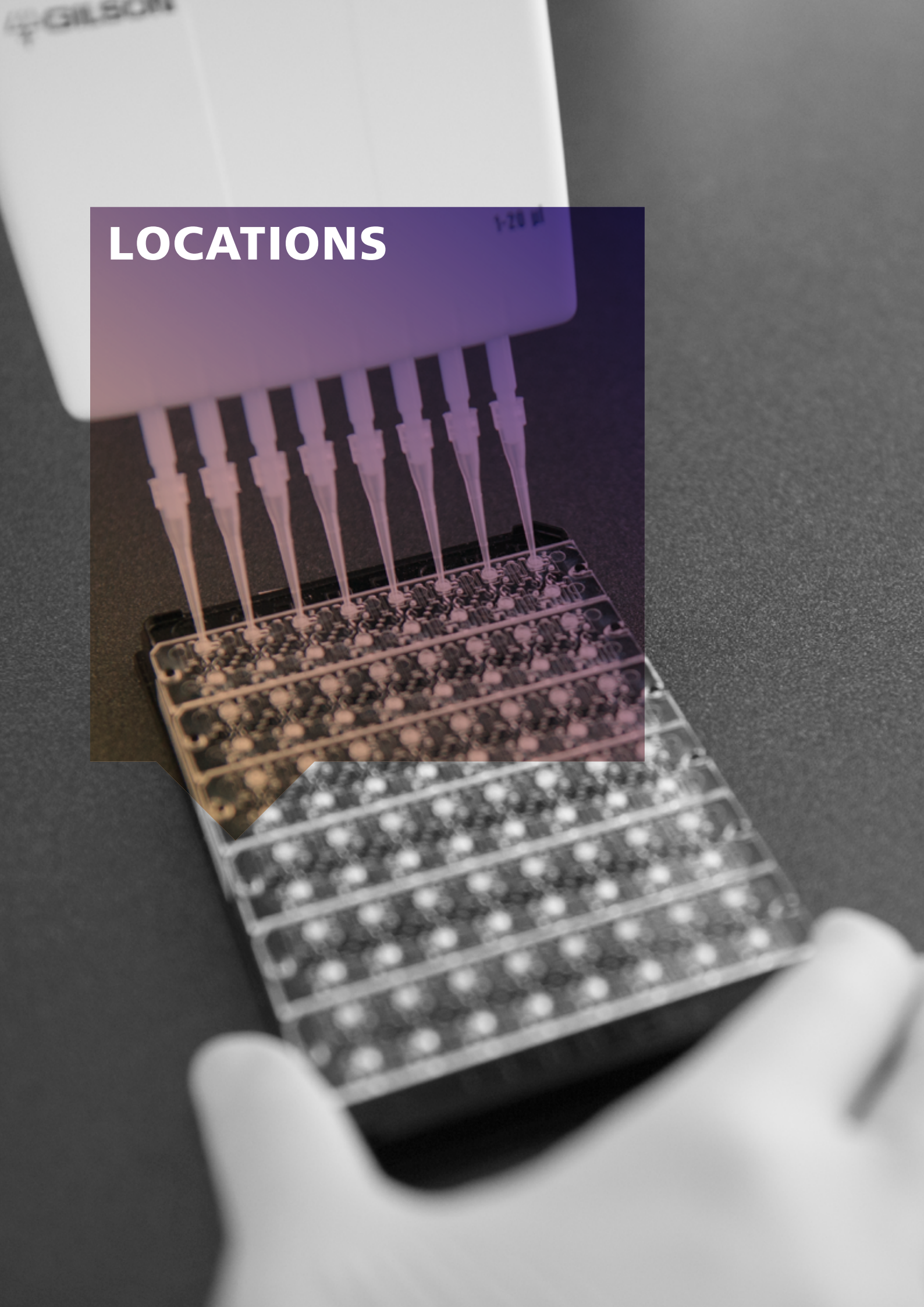

HEADQUARTER

LEIPZIG, SAXONY, GERMANY

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.

FACTS

- Address: Perlickstraße 1, 04103 Leipzig, Germany
- Usable area: 8 749 m²
- Employees: 443
- Focal areas: Cell engineering, cell therapy, drugs, diagnostics, immunology

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BRANCH BIOANALYTICS AND BIOPROCESSES

POTSDAM-GOLM, BRANDENBURG, GERMANY

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

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

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

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

FACTS

- Address: Am Mühlenberg 13, 14476 Potsdam-Golm, Germany
- Usable area: 4 096 m²
- Employees: 118
- Focal areas: Biotechnology, bioproduction, bioanalytics, automation

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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.

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 (biologicals). 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.

FACTS

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

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DEPARTMENT OF EXTRACORPOREAL IMMUNOMODULATION

ROSTOCK, MECKLENBURG-WESTERN POMERANIA, GERMANY

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

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BRANCH LAB TRANSLATIONAL CELL THERAPY

HANNOVER, LOWER SAXONY, GERMANY

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 CENTER MICROELECTRONIC AND OPTICAL SYSTEMS FOR BIOMEDICINE

ERFURT, THURINGIA, GERMANY

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

INVOLVED FRAUNHOFER INSTITUTES

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

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JLCI – JOINT LABORATORY OF CHONNAM NATIONAL UNIVERSITY HOSPITAL HWASUN IN COLLABORATION WITH FRAUNHOFER IZI

GWANGJU, JEOLLANAM-DO, SOUTH KOREA

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.

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FURTHERANCE

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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.

Members of the advisory board:

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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 ground-breaking 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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