Fraunhofer

IZI

FRAUNHOFER INSTITUTE FOR CELL THERAPY AND IMMUNOLOGY IZI

ANNUAL REPORT 2013

ANNUAL REPORT
2013


2012

INTERVIEW WITH THE DIRECTOR PROF. DR. FRANK EMMRICH

In October, the institute set up a new department in nearby Halle / Saale. What topics will the department focus on and how will it add to the range of services offered by the institute? The institute has an excellent set-up in the core areas of cell therapy and immunology thanks to its existing units. However, it became clear that cell engineering, tissue engineering, and immunomodulatory products were missing the complementary expertise of classic drug developers. Besides this, we intend to expand our neurological focus towards the exploration, treatment and prevention of neurodegenerative processes.

These considerations led us to look for a suitable way of expanding our capacities both in terms of methodology and subject matter. We were lucky to find a solution which was practically on our doorstep, in Halle/Saale. Our colleagues there traditionally focus on protein modifying enzymes and the development of suitable inhibitors both at the university and also in a special facility belonging to the Max Planck Society. Furthermore, we also saw research potential in the company Probiodrug AG, which had planned to break off from part of its diverse research activities.

All of this pointed towards setting up a Fraunhofer IZI department in Halle, especially as we were able to appoint Professor Hans-Ulrich Demuth to head the off-site department in Halle: a colleague who is brilliantly established and highly experienced on an international level. The main task dealt with by the "Drug Design and Target Validation" department concerns the development of novel drug candidates for neurogenic and immunological diseases. Alongside this, the department will also offer development modules through to the computer-based calculation of molecule optimization on a contract basis. The department's goals are excellently complemented by the medical indications and also the range of methods available at the parent institute in Leipzig. Although the department only got to work in October, by the new year it already had 28 members of staff and is set to grow further thanks to the acquisition of additional, third-party funds. We are extremely pleased to have been awarded special funding in the sum of 16.2 million euros from the State of Saxony-Anhalt for the first five years. This will help us quickly gain visibility at an international level and acquire valuable development contracts.

The Fraunhofer IZI organized the World Conference on Regenerative Medicine once again from October 23 – 25. What was your personal impression and which trends could be spotted? The WCRM 2013 was frequented by a higher number of attendees and there was much greater international diversity, reflected by the participation of over 50 countries. The conference was put together with the special relationship with Canada in mind. Newly appointed Canadian ambassador Marie Gervais-Vidricaire, who was able to be brought on board as guest of honor, gave a welcome speech. In an international communications experiment, the WCRM was connected to the Till McCulloch Meeting in the Canadian town of Banff, which was being held at the same time. This meant that talks and even discussions were able to be transmitted across the Atlantic. Besides this, five scholarships were awarded in each country to demonstrate the

partnership's mutual support for the next generation of scientists and to reinforce the amicable cooperation. A special highlight which had an impressive turnout was the European Medicines Agency (EMA) workshop, organized by the TRM Leipzig and held right at the start of the WCRM. Members of the Committee for Advanced Therapies (CAT) talked about their experiences with European marketing approval and the respective preparation work for advanced therapy procedures in the area of cell therapy and tissue engineering.

The first extension building was ceremonially inaugurated at the start of the year. The construction work for the institute's next building phase began shortly afterwards. How is the new research infrastructure shaping up and which strategic developments has it given rise to? The first Fraunhofer IZI extension building closed the gap between the main building and building section 5 of the BIO CITY on Zwickauer Straße. The institute has been successfully operating its first GMP facility for cell technology there since 2007. This is now connected to the uppermost level of the new building and with the staff offices in the main building via two bridges at the same level. Besides an entire floor dedicated to technology, the extension building also contains laboratories for research projects in systems biology and animal experimentation both at ground and basement level. This represents a considerable expansion of the laboratory area for the Cell Therapy department, which has moved into the new facilities. Thanks to the treatment and diagnosis stations for large animals on the ground floor, the Fraunhofer IZI has gained a special area of competence which, in connection with the neighboring Faculty of Veterinary Medicine, offers outstanding conditions for international cooperation projects.

As early as spring 2013, we were able to lay the foundation stone for the next structure, the second extension building. Once again, through the fantastic support provided by the City of Leipzig, the Fraunhofer IZI received a leasehold for a plot of land which has allowed us to build an additional laboratory on Perlickstraße between the main building and the BioCube. This will be almost the same size as the main building and will also be connected to the main building through a number of passages. Besides modern laboratories for GLP and GMP work and a special S3 laboratory for vaccine development, this building is especially distinguished by its "marriage stations" for joining biomedicine with biotechnology.

Here, the focus will predominantly be on developing automated cell technology devices, which will support the development of new diagnostic and therapeutic procedures. Both the first and ground floors will feature glass showrooms where respective development processes and the application of cell technical device combinations can be observed. This will make the institute more transparent and attractive for visitors, international partners, customers and also advanced training events.

What other achievements relevant to the institute would you like to highlight here? At the start of 2013, we were able to celebrate the opening of a joint laboratory (JLCI – Joint Laboratory of CNUHH in collaboration with Fraunhofer IZI) together with the Chonnam National University in Gwangju, South Korea, on the campus of Hwasun University Hospital near Gwangju. This strengthened our collaborative work and, above all, staff exchange between the two partners. Our next task is to acquire the South Korean pharma and biotech industry as a new customer.

The Fraunhofer IZI's international contacts are not just located to the east, but also to the west in the traditionally strong biotechnology and pharmaceuticals industry in North America. Following a number of talks at various respected

universities, we managed to find a highly reputable partner in the McMaster University in Hamilton – one of Canada's top three universities. Initial outcomes of the successfully initiated joint projects are being prepared for publication and new projects are already lined up. We expect to soon be developing interesting service offers for the extremely vibrant biotech industry scene in the province of Ontario, not far from the great lakes, and in the north-eastern US federal states.

Prof. Dr. Frank Emmrich

HIGHLIGHTS 2013

WORLD CONFERENCE ON REGENERATIVE MEDICINE

The Fraunhofer IZI held the World Conference on Regenerative Medicine for the fourth time from 23 – 25 October 2013. Over 1,000 international leading experts in the fields of research, clinical medicine and industry met in Leipzig to discuss the latest developments in regenerative medicine. Over 50 different nations were represented at the event, vouching for the global interest in the interdisciplinary research area.

The conference comprised over 205 talks and 270 poster presentations, in which renowned researchers and up-and-coming scientists described their current work from within the various sub-areas of regenerative medicine. The focus lay on the fields of stem-cell research, biomaterials, tissue engineering and cell therapy. However, molecular and immunological bases as well as regulatory and economic aspects were also intensively discussed. The organizers were once again able to identify a huge interest among industry representatives. For example, Pfizer/Neusentis supplemented the scientific program with a session on the topic of disease modelling and drug discovery using stem cells. In special sessions, other companies debated issues surrounding automated manufacturing and concerning the logistics of cell-therapy products.

The 2013 conference was very much influenced by the partnership with Canada, which is also home to a vibrant research scene in terms of regenerative medicine. The partnership was reinforced through various joint initiatives in cooperation with Canadian partner institutions such as the Centre for Commercialization of Regenerative Medicine (CCRM) and the Canadian Stem Cell Network. The famous Till & McCulloch Meeting thus took place at the same time in the Canadian town of Banff. Both countries each sent five junior scientists to the partner conference. Keynote speeches given by Peter Zandstra (CA) and Michael Cross (DE) were transmitted using video conference technology. The ceremonial address on the opening evening of the conference also featured one of the most reputable stem cell researchers from Canada, Mick Bhatia.

The interdisciplinary event boasted an extremely wide range of scientific insights. It confirmed the fact that pharmaceutical development is looking more and more towards the use of stem cells. Applications in the field of drug development and toxicity tests were discussed in particular depth. Commercial exploitation in these areas is expected to be seen much earlier than therapeutic application. Furthermore, it was evident that regenerative medicine, especially in terms of bone and cartilage regeneration, has already made its way into the everyday clinical setting. In particular, applications based in the fields of tissue engineering and biomaterials are proving to be more and more successful in the reconstruction of bone and cartilage defects.

An additional highlight was an integrated workshop on regulatory issues concerning the authorization of cell-based therapeutic products, which was organized jointly by the Committee for Advanced Therapies (CAT), the European Medicines Agency (EMA) and the Translational Centre for Regenerative Medicine (TRM) at the Leipzig University.
It is not easy for small and medium-sized businesses to meet the requirements of a Europe-wide authorization procedure. This is the main reason for the low number of EMA authorizations which have so far been granted for Advanced Therapy Medicinal Products (ATMP). A Europe-wide survey carried out by the CAT showed, however, that more than 300 ATMP products and procedures are currently being prepared for EMA authorization.

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EXPANDING THE RESEARCH INFRASTRUCTURE

On January 23, 2013, the Fraunhofer IZI celebrated the opening of its first extension building. Work on the third construction phase began shortly afterwards and the building was topped out on December 11, 2013.

After nearly three years under construction, the new building was handed over as early as the end of 2012 and partly put into operation. The new building was then officially presented and ceremonially inaugurated at the beginning of January. Around 250 guests from the fields of research, politics and business joined in the celebrations. Saxony's Minister-President, Stanislaw Tillich, opened the ceremony with words of praise and described the Fraunhofer IZI as a driving force in Saxony's innovation engine. Mayor Burkhard Jung also attended the opening and congratulated us on the successful cell division.

The new building is located between BIO CITY, where the Fraunhofer IZI still operates a clean room facility for manufacturing cell-based therapeutic products, and the institute's main building. Bridges on the first and third floors and a basement corridor connect the neighboring buildings. New therapy concepts can now be developed and tested over 1,200 m² of additional laboratory space.

Laboratories for experimental medicine are located in the new building, where new forms of therapy for treating neurodegenerative diseases such as stroke will be developed and tested on small and large animal models. Through the extension, laboratory capacities for molecular and cell-biological work have been increased and the research infrastructure has gained additional imaging technologies, such as laser scanning microscopy, bioluminescence imaging and a 7-tesla small animal MRI system. In addition, the institute's clean room capacities have been expanded by a second approx. 410 m² GMP facility. Construction costs, including initial fittings and furnishings, amounted to a total of 10.8 million euros. 60 per cent of this amount was funded by the European Union, whereas the Federal Government and the Free State of Saxony contributed 20 per cent each.

Construction work for the third building phase, which will round off the institute's infrastructure, began in spring. With over 3,200 m² of floor space, the second daughter cell will be almost as big as the main building, which it will also be connected to via bridges. Besides additional laboratory and clean room capacities, the new building is to also be equipped with a technical center which will optimize processes in cell-oriented medical technology. The third and, for now, final building phase is planned for completion in spring 2015.

1 *First extension building (view from BIO CITY)*
2 *Construction site of the third building phase (view from Perlickstraße)*

NEW DEPARTMENT IN HALLE

The Fraunhofer IZI set up a second department on July 1, 2013. The new site in Halle / Saale complements the institute's service portfolio in the area of molecular drug discovery and development.

The development of new therapies and drugs is one of the Fraunhofer IZI's core competencies. Besides cell-based therapeutic procedures, the institute also develops and tests vaccines and various classes of drugs, primarily in the areas of infectious, inflammatory and oncological diseases. The addition of the department in Halle has expanded and complemented expertise in the fields of low-molecular and antibody-based drugs.

One of the group's special areas of competence lies in identifying pathological mechanisms at protein level and optimizing drugs based on the respective findings. With this expanded service portfolio, the institute is addressing the pharmaceutical and biotechnological industries in particular: it is to act on behalf of or in cooperation with these industries to develop new drugs and drug discovery test systems.

Benefiting from close ties with the academic and industrial establishments in Halle, the department was optimally integrated into the infrastructure from the very beginning. This meant it was able to recruit 28 exceptionally qualified members of staff by the end of 2013. The site is managed by biochemist Professor Hans-Ulrich Demuth. Professor Demuth spent many years leading a "Drug Discovery" working group, initially at the Martin Luther University of Halle-Wittenberg and later at the Leibniz Institute for Natural Product Research and Infection Biology in Jena. During his time as Chairman of the Board at the biotech company Probiodrug AG, his team developed a concept for treating maturity-onset diabetes which is available on the market today.

Fraunhofer IZI's off-site department is currently located in laboratories and rooms of the Bio-Centre on the Weinberg Campus in Halle. The five-year start-up phase is being supported by 16.2 million euros of funding from the Federal State of Saxony-Anhalt and from the European Regional Development Fund (ERDF). Mid- and longterm goal of the new department is to receive funding through third-party funds, industry contracts and income from license agreements.

1 *Handover of the sponsorship approval letter from Minister-President Rainer Haseloff to the President of the Fraunhofer-Gesellschaft, Professor Reimund Neugebauer*

2 *Congratulations to Professor Hans-Ulrich Demuth from Professor Reimund Neugebauer and Professor Frank Emmrich*

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FRAUNHOFER IZI EXTENDS INTERNATIONAL COOPERATION

As part of a widespread internationalization strategy currently being followed by the Fraunhofer IZI with the aim of entering new markets and ultimately fostering the institute's profit situation, the institute is also involved in projects in Canada and South Korea. Together with outstanding research partners, both the Asian and North American markets are to be gradually made accessible.

Canada

With an excellent research landscape in the field of life sciences and a vibrant biotechnological and pharmaceutical industry, Canada is an exceptionally interesting market and cooperation partner for the Fraunhofer IZI. The institute has found a noted partner in the McMaster University in Hamilton, Ontario province: besides numerous points of intersection between the university and the Fraunhofer IZI's research fields, the university also boasts excellent links to local industry players. Thanks to the intensive support received from the Canadian embassy in Berlin, the institute was already able to establish a close cooperation with the McMaster University back in 2011, which was further expanded on and consolidated in 2013. Following several representative missions, this led to the conclusion of a cooperation agreement, which forms the basis of future collaboration work in various projects.

Since autumn 2013, as part of two pilot projects, researchers from both partner countries have been collaborating on developing new immune therapies to treat cancerous diseases as well as on innovative technologies to more efficiently diagnose tuberculosis. This will be followed by additional projects in the fields of vaccine development and dyslexia research. The aim of the joint efforts is to set up a Fraunhofer project center in Hamilton over the next few years, which will facilitate an even more intensive cooperation with local research institutes and Canadian companies.

The joint projects will focus on "Bioengineering" and the "Advanced Manufacturing" of products for diagnostic and therapeutic applications.

1 *Signing of the cooperation agreement at the McMaster University in Hamilton, Ontario province, Canada*

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Korea

For us here in Europe, the Asian markets appear no less foreign and closed at first glance than their cultures. And yet these markets are undergoing hugely dynamic developments, especially in the field of life sciences. However, without the presence of partners in the respective country, it is difficult to start up cooperations in Asia: not only because of the linguistic and cultural obstacles, but also as the economic structures tend to be difficult to penetrate. South Korea is classed as one of the fastest growing markets; its potential for development is therefore extremely promising.

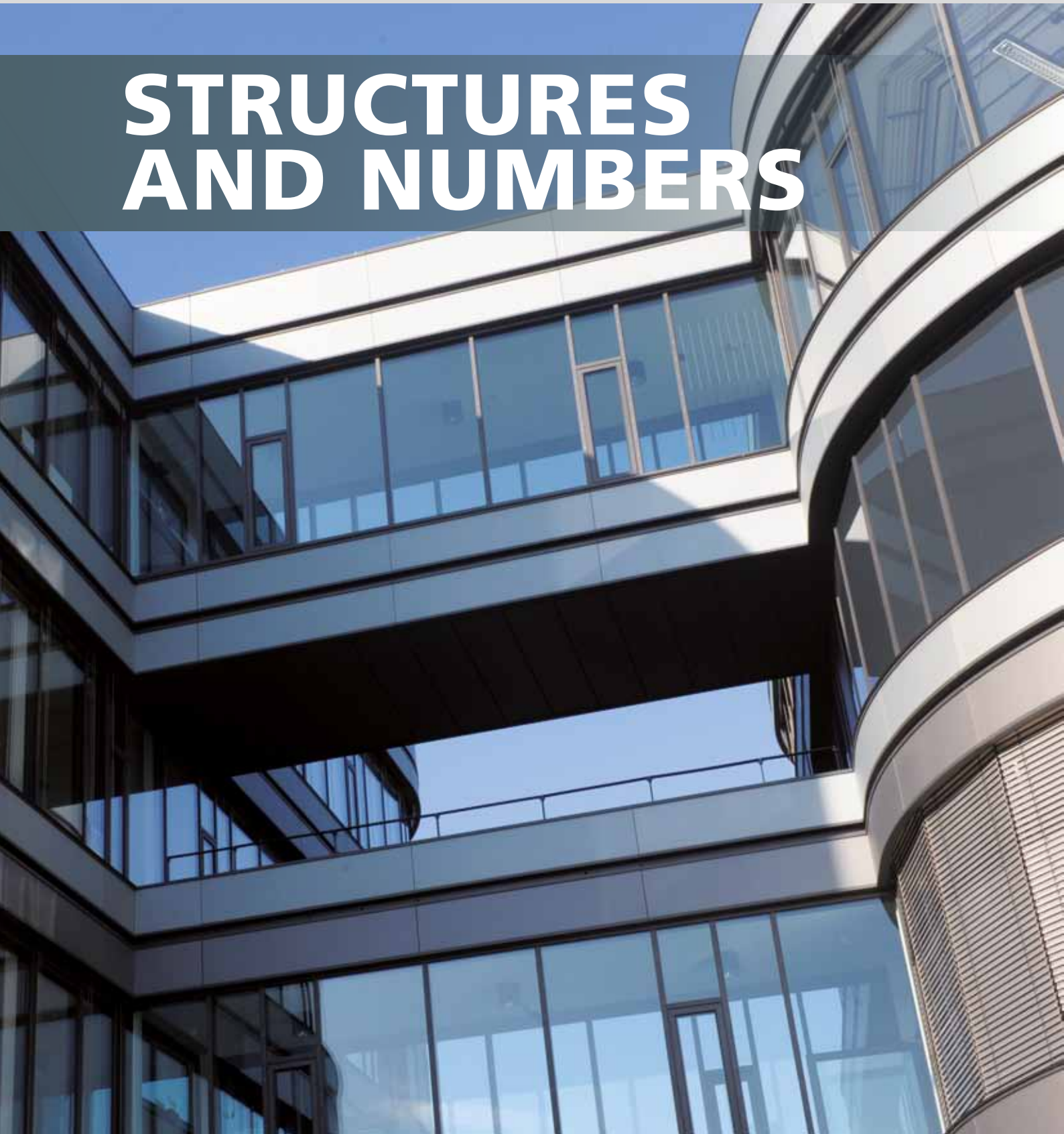
Together with the Chonnam National University Hwasun Hospital (CNUHH), the Fraunhofer IZI started talks back in 2010 which led to a successful application for state funds in 2011. With over 600 beds, the CNUHH is one of the largest and most modern cancer clinics in South Korea. Following several researcher exchange programs and intensive work to secure funds, many more key milestones were able to be achieved in the 2013 reporting year. These include founding a joint research laboratory in Hwasun, around 20 km south of the metropolis Gwangju. The laboratory is located in the hospital's Cancer Research Center on an expanding, new campus which belongs to the University of Gwangju. By 2017, the facility will be co-financed through the Global R&D Centers' program (GRDC) run by the Korean National Research Foundation. The joint laboratory provides both the legal and infrastructural parameters for conducting joint research projects. The emphasis here is on developing new procedures to diagnose and treat cancer.

On December 4, 2013, the Fraunhofer IZI in Leipzig held what was already the fourth collaborative workshop, as part of which the current state of research on both sides could be discussed. In future, the joint laboratory will gradually be expanded to include more projects and colleagues.

Peptide libraries belonging to the Fraunhofer IZI will be used in the joint projects and a technique for treating tumors using controlled bacterial infections, which was designed at the CNUHH, will also be advanced.

1 *The Korean delegation visiting the Fraunhofer Institute for Cell Therapy and Immunology*

STRUCTURES AND NUMBERS



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.

Over the past years, biotechnology and regenerative medicine have taken on greater significance. Of these specialized fields the public expects new therapies for the treatment of diseases which lead to the irreversible damage of tissue and organs; these invariable include chronic, autoimmune and tumor diseases.

The goal is to systematically repair the damages caused by diseases associated with the destruction of cells or tissue and to correct dysfunctions by means of cell therapies, tissue engineering or targeted modulation of the immune system. This goal can be achieved by stimulating the body's own regeneration processes or by means of biological substitutes in form of extracorporeally cultivated tissues.

General topic: Cell therapy and immunology

In the narrow sense of the word, cell therapy denotes the transfer of cells that provide a substitute for lost functions however are also capable of taking over advanced active functions and additionally the term describes the repairing of defects by means of treatment with cells. Stem cells can be transferred in order to induce the formation or repair of tissue.

This builds a bridge to immunology, which is concerned with cellular defense and control mechanisms. It is expected that cell therapeutic methods for targeted enhancement, suppression or regeneration of the immune system will soon be available, e. g. for stimulating the defense mechanisms of degenerate cells or for suppressing undesired graft-versus-host reactions against grafted tissue. In addition, the further development of immunomodulatory techniques, e. g. vaccination, is of particular importance.

The institute's tasks

The institute comprises the four departments of Cell Engineering, Immunology, Cell Therapy and Diagnostics. Furthermore, the Fraunhofer IZI is operating two branch labs in Rostock and Halle/Saale. Assigned to these departments are a total of 21 units having a broad spectrum of competencies and qualifications.

The institute's spectrum of services is aimed at specific problem solutions at the interfaces of medicine, biosciences and engineering.

With this, the Fraunhofer IZI addresses not only the biomedical industry, including pharmaceutical and biotechnological companies and diagnostic laboratories, but also hospitals and research facilities.

The core competencies are concentrated in the field of regenerative medicine, which in addition to the development and testing of new agents also specifically includes cell therapeutic approaches to the regeneration of dysfunctional tissues and organs through to biological replacement with tissues cultivated in vitro (tissue engineering). For an unproblematic engraftment of these tissues it is necessary to detect cellular and immunological mechanisms of defense and control and to integrate them into the development of methods and products. Around these core competencies a large variety of tasks for new products and methods arises. The institute is strongly oriented towards the hospitals and takes on quality testing, the production of clinical test samples according to GMP guidelines and contracted clinical trials. In addition, we support our partners in obtaining manufacturing and marketing authorizations.

ORGANIZATION

The institute breaks down into five departments, all of which are then organized into different units. Scientific services are supported by the administration and the executive departments "Business Development and Patent Management" and "Press and Public Affairs".

Business Development and Patent Management

The Fraunhofer IZI considers itself to be a professional service provider in the field of research and development. Numerous industry and service companies, as well as public contracting authorities, constitute our client base. Furthermore, the institute cooperates with various academic and non-academic research institutes in developing innovative technologies.

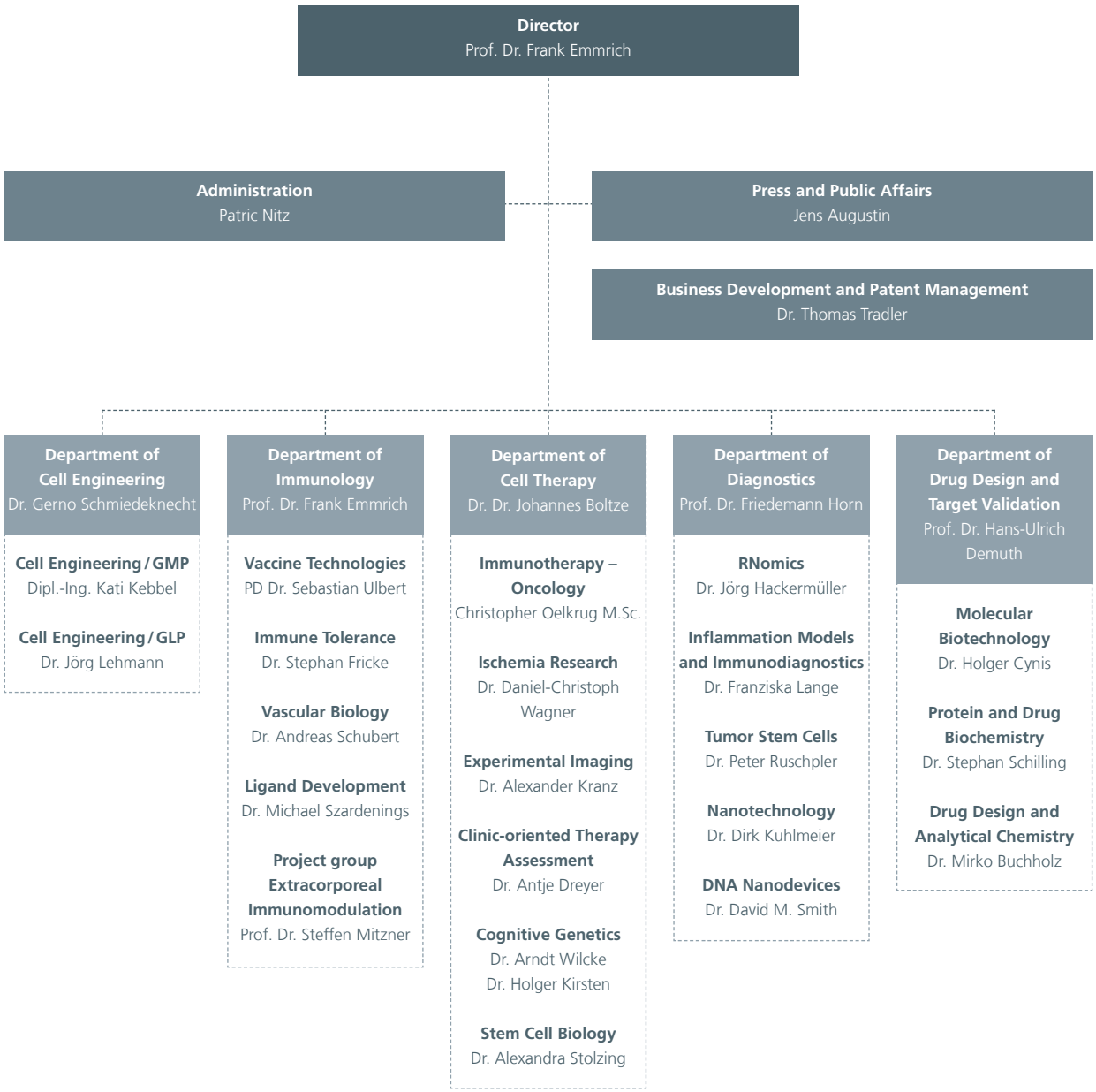
The institute is particularly proud of the ability to offer its clients a varied and wide range of services within the fields of drugs, cell therapy, diagnostics and biobanks. The executive department "Business Development/Patent Management" sees itself as a central point of reference in terms of communicating the most suitable services to clients and partners.

Press and Public Affairs

As an institution of applied research, the Fraunhofer IZI places great value on information provided by clients and the public. The executive department "Press and Public Affairs" coordinates the institute's internal and external communication. Through publicity events, the department assumes the institute's responsibility to inform and enlighten the public with respect to ongoing research. Furthermore, the executive department organizes the annual "Fraunhofer Life Sciences Symposium" and the biannual "World Conference on Regenerative Medicine". Through both these events, the institute promotes scientific exchange and particularly helps to bring together the different research disciplines involved in regenerative medicine.

Administration

The lean and efficient administration of the Fraunhofer IZI is broken down into the departments IT, technology and business administration. Together with an external service provider, the IT department looks after the entire infrastructure. Through proficient in-house activities, cost-effective procurement of spare parts, and a series of energy-related optimizations within the areas of equipment and building technology, considerable savings were made with regards to operating costs. Through increased regulations and commercial processes within the areas of travel, procurement and personnel, the workload has increased in the business administration area. This challenge was addressed by further training and expansion of skills in order to make full use of employees' potential.


Director
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Drug Design and Analytical Chemistry
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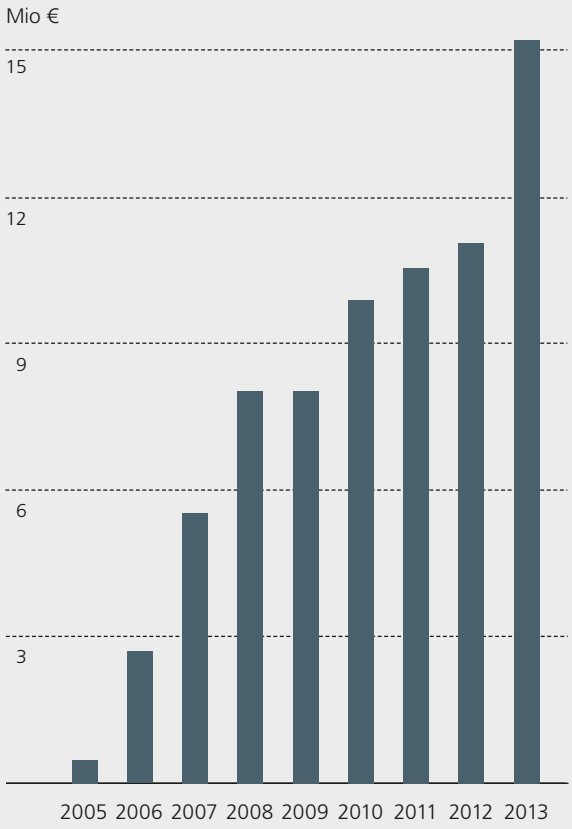
THE INSTITUTE IN NUMBERS

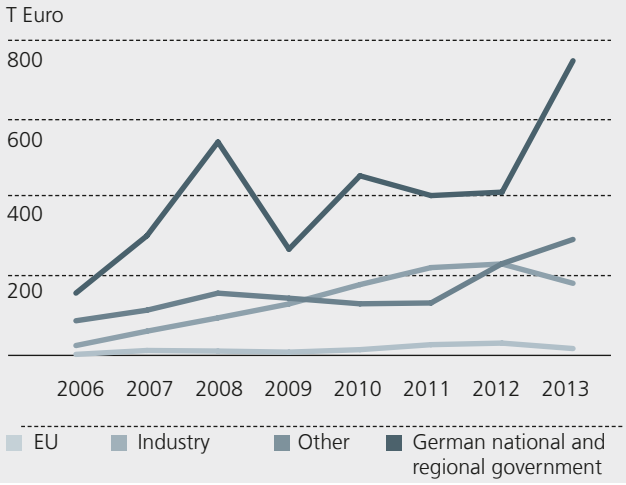
Financial value



Overview of the projects

	number 2013	volume 2013
German national and regional government	20 (38 %)	7,484,000 €
EU	2 (4 %)	163,000 €
Industry projects	18 (35 %)	1,823,000 €
Other (incl. internal programs)	12 (23 %)	2,939,000 €
Total	**52**	**12,409,000 €**

Projects by volume



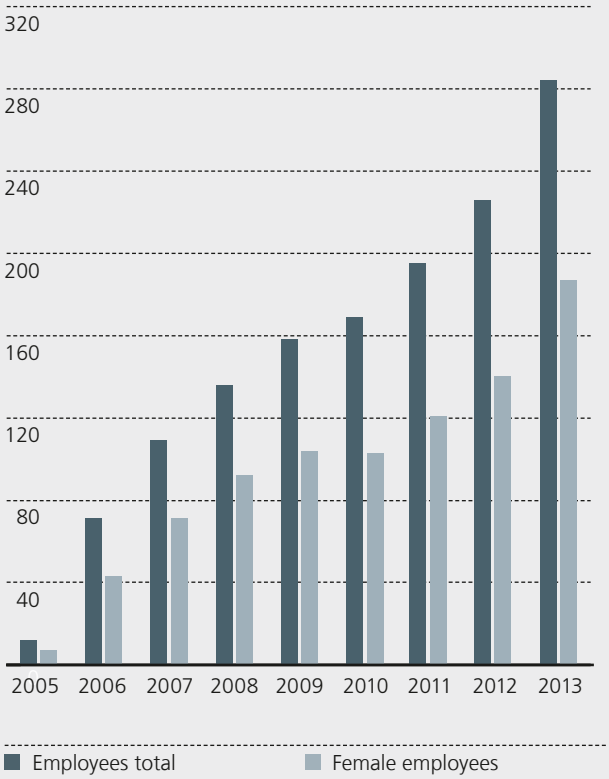
Financial value

Our financial value again increased significantly to over 15 million euros. This takes into consideration the Halle-based Drug Design and Target Validation department for the first time. Expenditure for the major building works is not included. They are being financed by the Free State of Saxony, the Fraunhofer-Gesellschaft and the European Union.

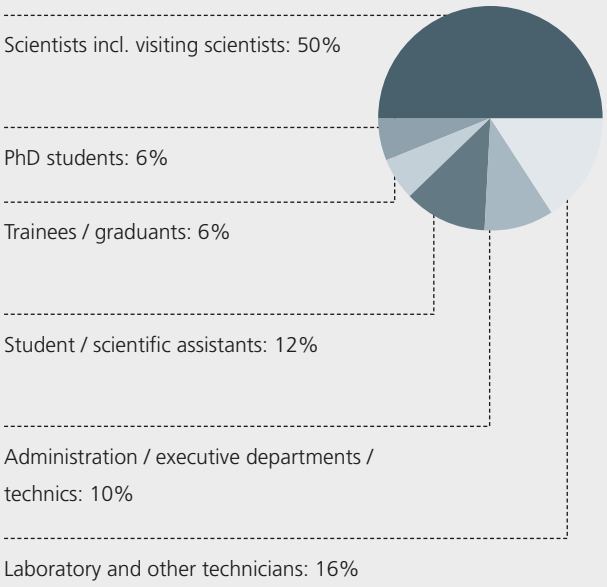
Projects

The profits from publicly funded projects were able to be further increased in 2013. This can be put down to new research initiatives. Besides partaking in traditional industry projects, the institute lends a significant amount of support to industrial cooperations which are funded through the Sächsische Aufbaubank (Saxon Development Bank, SAB) using means provided by the federal state and the EU. In many cases, these cooperations have given way to follow-up projects and settlements. As the partner companies have to bring in co-financing of between 40 and 70 %, these projects hold a special position in the institute. They are not classed as industry projects.

Employees



Workforce composition

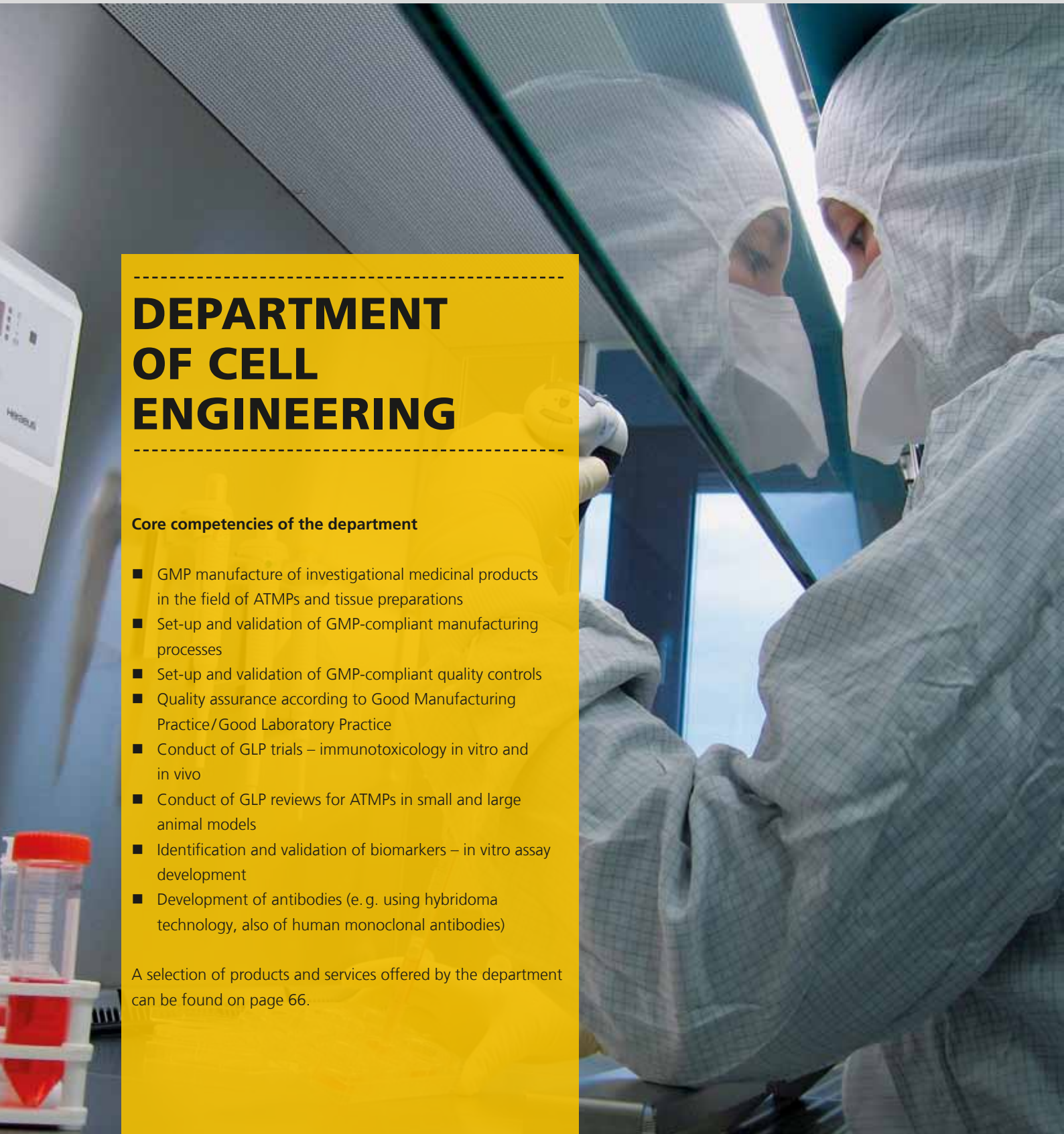


Employees

In 2013, the Fraunhofer IZI experienced a record growth rate in its workforce. Compared with the same period in the previous year, the number of employees at the institute increased by 25 %, reaching 284 members of staff by the end of the year. This figure does not include the 60-plus guests who worked on various projects at the institute for short periods of time. The most growth was recorded among scientific and technical staff, who are entrusted with research and development tasks. This dynamic development forms the basis of scientific excellence, the continuous promotion of young scientists, and the sustainable consolidation of partnerships both in Germany and abroad.

Interdisciplinary and intercultural teams help maintain highest quality results. With 18 branches of study, our staff's qualifications are as diverse as their cultural backgrounds.

The number of employees from abroad also rose by 7 % What is also notable is the high percentage of female employees: the Fraunhofer IZI takes top place in this respect compared with the other institutes in the Fraunhofer-Gesellschaft.



DEPARTMENT OF CELL ENGINEERING

Core competencies of the department

- GMP manufacture of investigational medicinal products in the field of ATMPs and tissue preparations
- Set-up and validation of GMP-compliant manufacturing processes
- Set-up and validation of GMP-compliant quality controls
- Quality assurance according to Good Manufacturing Practice/Good Laboratory Practice
- Conduct of GLP trials – immunotoxicology in vitro and in vivo
- Conduct of GLP reviews for ATMPs in small and large animal models
- Identification and validation of biomarkers – in vitro assay development
- Development of antibodies (e. g. using hybridoma technology, also of human monoclonal antibodies)

A selection of products and services offered by the department can be found on page 66.

IN CONVERSATION WITH DR. GERNO SCHMIEDEKNECHT

What particular challenges did the 2013 reporting year have in store for the Department of Cell Engineering and what is the outlook for 2014? The greatest challenge of 2013 came with the commissioning and GMP-compliant qualification of the new clean room facility in the Fraunhofer IZI's first extension building. Carrying out this work required numerous external service providers to be coordinated, a range of risk analyses to be drafted and checked, validation plans and reports to be written, and the existing quality assurance system to be expanded to include the newly added rooms, equipment and procedures. All of this had to take place during business hours, which meant at the same time as production and quality controls for active clinical trials, which were being conducted on behalf of our customers. As we were unable to bring in additional members of staff for this work, my colleagues found themselves facing an enormous workload. I would like to take this opportunity to thank them once again for all their efforts. Besides this, following complex preparatory work and authorization procedures, a real highlight of 2013 was when we started to manufacture and conduct quality controls for investigational medicinal products with regard to two of our key projects: CVac™ on behalf of Prima BioMed Ltd. and DCVax®-L for Northwest Biotherapeutics Inc./Cognate BioServices Inc. The next challenge is already in sight for 2014 in the construction and qualification of an additional cell-therapy clean room facility in the Fraunhofer IZI's second extension building. An important milestone for the Cell Engineering/GLP unit was the start of a Fraunhofer-internal preliminary market-oriented strategic research project entitled LowAllergen. The LowAllergen project creates the foundations for manufacturing food ingredients which contain reduced allergenic properties: a topic set to gain significance in coming years.

The department offers numerous services relating to quality management. Which development services stand out as being in especially high demand within the industry? There is a particular demand among industry players for the manufacture and quality control of cell-based drugs for clinical trials, carried out in full compliance with GMP. The Cell Engineering/GMP unit has progressed to become one of the leading European providers in this area, placing special emphasis on autologous therapeutic approaches. Interestingly, demand in this area is especially prominent among international customers, predominantly from the USA but also from other European countries. This may well be due to the fact that, compared with Germany, these countries have easier access to the capital market, especially to venture capitalists. The services offered by the Cell Engineering/GLP unit regarding the preclinical testing of cell-based drugs, especially with respect to demonstrating safety and harmlessness, are also enjoying increasing popularity and are therefore in the process of being boosted, internationalized and provided to a wider target group.

In 2013, the department assisted with various clinical trials in collaboration with a number of international partners and clinics. How is this type of cooperation, involving so many different international partners, structured? Cooperating with so many international partners presents new challenges every day. The majority of what is communicated on a daily basis, and also the respective documentation, is in English, which poses a learning process especially for our young colleagues who are new to the department. In addition, international customers often have other cultural backgrounds and thus a different understanding of the nature and scope of communication, the way in which projects are processed, operating principles, or the time lines assigned to a project. It is not always easy to satisfy these different ideas, or to adapt them to the processes in place in Germany, which results in pragmatic compromises constantly being suggested and negotiated. Other than these interpersonal aspects, drafting contracts also involves a huge amount of work: this begins with choosing the legal status and ends with taking into account the laws, which to some extent are hugely divergent within Europe alone in the field of drug manufacturing.

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UNITS

Cell Engineering / GLP Unit

The unit focuses on three main topics: 1) Planning and conducting preclinical efficacy and safety studies for new drug candidates, in particular ATMPs, (in vitro and in vivo) under GLP and GLP-analogous conditions. This also includes the development, establishment and validation of new in vitro and in vivo models. 2) Identification and validation of new protein biomarkers for application in diagnostics and in the treatment of chronic inflammatory and tumor diseases as well as for veterinary medicine/animal breeding. 3) Developing and optimizing methods and techniques for the diagnostic detection of protein biomarkers and for the separation of cells. This includes the development, manufacturing and modification of monoclonal antibodies as well as participation in the development of analytical equipment and cell separation robots.

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Cell Engineering / GMP Unit

The Cell Engineering/GMP unit operates Fraunhofer IZI's two modern GMP clean room facilities consisting of eight separate clean room suites (altogether 16 clean room grade B manufacturing rooms) which are optimal for manufacturing Advanced Therapy Medicinal Products (ATMPs). The 60 highly qualified staff members specialize in the GMP-compliant manufacturing and quality control of investigational medicinal products. Transfering and establishing GMP-compliant processes and quality controls as well as creating Standard Operating Procedures (SOPs) are discussed in detail with the partner at the start of the project and then implemented in practice, with a strong emphasis on quality. Project leaders have many years of experience in designing GMP-processes in the cell therapy area.

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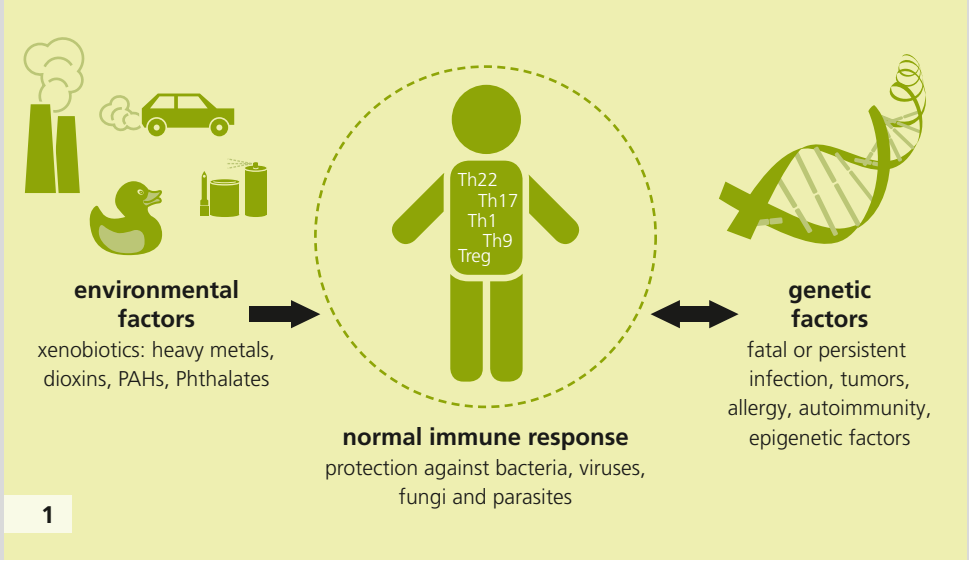

1

PROJECT EXAMPLES

Establishing a mouse model to investigate the immunomodulatory effects of xenobiotics and pharmaceuticals on the immune response in the context of an infection. Subproject 1: investigating the effect of benzo[a]pyren (BaP) on the protective type-1 immune response against Salmonella enterica

The environmental toxin BaP is primarily known as a causative agent for the development of mutations and cancer. In the past few years, however, immunomodulatory effects could also be demonstrated in numerous studies. In these studies, the carcinogenic and most likely also the immunomodulatory effect was primarily mediated through the AhR transcription factor, which is activated upon interaction with BaP. The gene products of the various target genes are involved in processes regulating apoptosis, the cell cycle and the immune response. As part of this project, the influence of extremely low subtoxic concentrations of BaP were investigated and characterized in more detail, especially with regard to the activation of macrophages through bacterial stimuli. This meant conducting exposure tests in vivo, ex vivo and in vitro in order to demonstrate potential modulation by subtoxic concentrations of BaP. The in vivo tests in the murine salmonella infection model showed that mice that were administered BaP in subtoxic doses on a weekly basis demonstrated up to a 60 per cent higher survival rate compared with control animals. Nevertheless, the animals treated with BaP were unable to eliminate the salmonellae in a sterile way. During the course of the infection, the animals treated with BaP demonstrated higher salmonella-specific antibody titers (IgG2c, IgG1). Macrophages and neutrophilic granulocytes in the spleen and the peritoneal cavity expressed higher levels of FcγRI (CD64) and MHC class II (IAb) when influenced by BaP. Furthermore, peritoneal cells exhibited an increased NO synthesis rate.

The BaP-dependent changes observed in the in vivo infection model could be mostly recapitulated in vitro. In antigen-stimulated bone marrow macrophages, BaP brought about an increased NO synthesis rate as well as an elevated expression of functional markers such as MHC-II (IAb), CD64, CD14 and CD86. Furthermore, BaP caused a decrease in the secretion of the cytokines IL-1β, IL-12, IL-6 and TNF-α in these cells. The cytokine IL-10, in contrast, was secreted in higher amounts under the influence of BaP. Analogous to these results, a lower mRNA expression of the genes Il1β, Il12, Il6 and Tnfα were detected after BaP exposure in transcription studies whereas an increased transcription rate was observed for IL10. In addition, an increased phagocytosis activity of cells treated with BaP was verified in bone marrow macrophages, as well as in the macrophage cell line RAW264.7. In summary it can be ascertained that BaP exposure suppresses the expression of proinflammatory cytokines, but induces the expression of the anti-inflammatory cytokine IL-10.

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1 *Factors influencing the immune response*

1

Development and application of novel on-farm techniques to monitor stability of health and fertility in German Holstein dairy cows

This project aimed to identify new immunological biomarkers in milk to characterize the general state of health of dairy cows. Using the identified markers, immunoassays were developed that can be directly used on the breeding farms ("on-farm"). Taking measurements from the milk produced directly in the cowsheds keeps the time and costs associated with the test to a minimum. This allows the entire herd to be tested and sick animals to be detected quickly and treated accordingly. Early recognition reduces the severity of diseases and increases the chances of a successful treatment. It also results in lower incremental costs arising from extended treatment periods. Moreover, it prevents the loss of milk yield or even the entire animal.

In order to gain an overall pool of potential biomarkers that are traceable locally in the udder, biomarkers were first searched for on the transcriptome level of milk cells. The results from the transcriptome analysis were then validated using a sensitive polymerase chain reaction (PCR) and the identified potential markers were then verified at protein level. In collaboration with the Helmholtz Centre for Environmental Research (UFZ), comparative proteome analyses from samples taken from different cows in various medical conditions were created using specific enzyme immunoassays.

Haptoglobin was identified as a particularly significant biomarker. So far, this main acute-phase protein has primarily been discussed as a mastitis marker. In addition, a further protein was identified in the milk which demonstrated a high demarcation capacity for highly inflammatory diseases. The surface molecule CD25 (cluster of differentiation 25) on bovine granulocytes was also identified as a suitable biomarker at a cellular level. The expression of CD25 on the cell surface appeared in increased amounts, depending on the severity of the disease.

In order to develop a robust test that can be conducted in the cowshed which is diagnostically conclusive even under changing environmental conditions, reagents and technologies now have to be adapted and optimized alongside the identification of new biomarkers for the verification of the latter. The aim is to develop an automated test procedure which will improve health and herd management on large agricultural farms.

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1 *It is hoped that a rapid test to characterize the health condition of dairy cows will prevent disease and sustain productivity.*

1

Pharmacological and clinical development of the CVac™ agent in a multicenter phase-IIb trial

The product CVac™ is an autologous, somatic cell therapeutic agent which is to be used as a supplementary treatment for tumor diseases. The therapeutic agent comprises dendritic cells which are loaded with the antigen mucin 1 (mannan fusion protein, M-FP). As part of the project, the safety and efficacy of the procedure is to be tested in the treatment of ovarian carcinoma. The project is being conducted on behalf of Prima BioMed GmbH, a subsidiary of the Australian company Prima BioMed Ltd. and is being funded through the Sächsische Aufbaubank (Saxon Development Bank).

Before this project could be carried out, the manufacturing process and quality controls first had to be transferred in their entirety from Australia to Leipzig. This included, among other things, preparing the necessary documentation in line with Good Manufacturing Practice (GMP), establishing all the procedures in the clean room area and/or quality control laboratory and validating the manufacturing process and analytical methods. Following a detailed inspection conducted by the pharmaceutical competent authorities, the Fraunhofer IZI was subsequently granted a manufacturing authorization in accordance with Section 13 of the German Drug Act (Arzneimittelgesetz).

However, further intensive preparations had to be made before the multicenter clinical phase-II CANVAS (CANcer VAccine Study) trial could commence. This involved, among other things, obtaining the necessary import permits for the active ingredient M-FP and for the placebo from Australia, as well as the qualification of numerous hospitals in the European Union and Eastern Europe, which provide the cellular base material for the manufacture of CVac™ by means of so-called leukapheresis. Furthermore, a comprehensive logistics system was set up which harmonizes and optimizes the manufacturing process together with other manufacturers in the USA and Australia, and accompanying quality controls were developed for the verification of efficacy in vitro. Once this preparatory work was complete and the clinical trial had been approved by a number of European supervisory authorities, the first European patients were able to be enrolled onto the trial in the Ukraine and Belarus in March. During the course of the year, the trial was then expanded to include additional countries, including Germany. The clinical trial will continue throughout the remainder of this year and into 2015. In addition, another trial involving CVac™ is planned for 2014 which looks at the indication of pancreas carcinoma.

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Europa fördert Sachsen.
EFRE
Europäischer Fonds für regionale Entwicklung

1 *Manufacture of Cvac™ in the clean room*

DEPARTMENT OF IMMUNOLOGY

Core competencies of the department

- Vaccine development
- Tolerance induction
- Antibody development
- Immunological models
- Ligand development
- Rheologic models
- Antimicrobial peptides
- Cellular adsorbers

A selection of products and services offered by the department can be found on page 66.

IN CONVERSATION WITH PROF. DR. FRANK EMMRICH

Which scientific areas did the department focus on in the reporting year? An important topic in the department is the targeted modulation of the immune system, this being its stimulation or suppression. On the one side, the immune response is to be specifically strengthened against particular pathogens by using vaccines in such a way that inoculated individuals are protected from infections. On the other side, an immune response against tissue which is extraneous to the body has to be prevented, or at the very least alleviated, in order to improve the integration and healing of transplants.

Huge progress was made in vaccine development last year. In cooperation with international partners, as part of a major EU joint project being coordinated by our institute, we have developed vaccination strategies based not only on proteins, but also on DNA. These vaccines defend against an infection with the dangerous West Nile Virus (WNV) and have successfully completed the preclinical development stage. Important milestones were also achieved in the case of immunosuppression using specific antibodies to prevent transplants from being rejected, which means that the therapeutic approaches can move into clinical testing. Furthermore, the department is focusing its attention on developing diagnostic methods. In doing this, optimized gene libraries are drawn upon to identify allergenic structures which can later be used to evaluate and reduce the allergy-triggering potential of foodstuffs. Besides this, we are developing systems to detect infections according to their specific pathogens.

Has the exploitation of your research work resulted in any particular successes? Last year a diagnostic test we developed was granted official authorization. The PRRS (porcine respiratory and reproductive failure syndrome) virus poses an extremely grave problem in pig farming and causes huge losses year upon year all around the world. The virus has many variants (genotypes). In order to be able to successfully fight PRRS using targeted control strategies such as vaccinations, the specific genotype of the infecting viral strain needs to be identified. This is where our test comes in. In contrast to the majority of methods presently available on the market, we have developed what is now a patented system that can be used to identify the genotype of the PRRS virus by focusing on the binding sites of special antibodies. We have a strong industry partner in Analytik Jena AG with whom we can continue to develop the test together. It has now been released for sale and we hope that it will also gain acceptance on the market. For the Fraunhofer IZI this symbolizes an extremely important step in the exploitation of our research findings.

Which technologies will be of particular significance in the department in years to come? Several interesting projects have been initiated thanks to the Fraunhofer IZI's international network, especially through partnerships with the Chonnam University in South Korea and the McMaster University in Canada. These are set to be developed further in the coming year. Such projects, for instance, look at developing strategies for the targeted transport of anti-tumor agents in cancer cells, or novel ways of diagnosing infections. Besides this, techniques to disable pathogens will also play a big role in vaccination development. A major Fraunhofer-Gesellschaft joint project on this topic will start in spring and be coordinated by our institute. Based on the preliminary work we know that our industry partners are highly interested in this project.

The institute's recently established animal laboratory is extremely beneficial and will play a key role in the department. We are now in a position to plan development work even better and conduct projects more efficiently.

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UNITS

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 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, molecular biology and immunology are well established in the unit. Viruses currently being focussed on include West Nile Virus, influenza, and PRRSV. In addition, large-animal models can be provided through the collaboration with the Faculty of Veterinary Medicine at the Leipzig University.

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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 animal models.

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Ligand Development Unit

This unit uses a new generation of peptide phage display libraries in combination with next generation sequencing. This technology is able to identify binding peptides even in complex mixtures, e.g. patient sera in the case of allergies or infections, new binding peptides for (cancer) cells as well as therapeutically or diagnostically relevant proteins. We aim to influence the immune system, find potential therapeutics and develop diagnostics and affinity purification ligands. In parallel, we investigate novel coupling methods for peptides; several patents have already been submitted in this area.

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Vascular Biology Unit

This unit aims to develop a preventative and at least partially curative gene therapy for arthrosclerosis. Using vascular models, genes and promoters are identified that can be activated by biomechanical forces such as using flows or stretching. As cardiovascular diseases are often induced by dental disease (caries, periodontitis), a second focus in the unit lies on establishing a treatment method against oral streptococcus.

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Extracorporeal Immunomodulation Unit

The unit focuses on the development and evaluation of extracorporeal (outside the body), organ-supporting 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, small and large 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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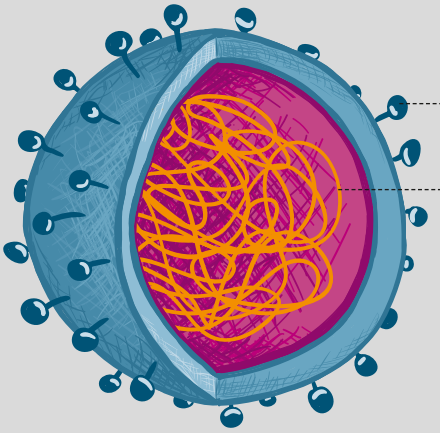

1

PROJECT EXAMPLES

Developing a vaccine to combat West Nile Virus

Viruses transferred by arthropods (such as mosquitos or ticks) count among the most dangerous infecting agents and are prevalent all around the globe. Many of these so-called arboviruses (arthropod borne) are zoonotic, which means they circulate among animals and are then transferred to humans by mosquitos, for example, where they can trigger life-threatening diseases. The West Nile Virus (WNV) is one of these types of zoonotic pathogens and has seen an enormous expansion of its area of distribution over the past 20 years – it is now endemic in several southern and eastern European countries. WNV can cause severe neurological symptoms in older people in particular and has led to hundreds of people becoming seriously ill and dozens of deaths in Europe alone since 2010.

Despite there being vaccines to protect horses from WNV, a vaccine has not yet been developed for human use. As vaccines used in veterinary medicine are not suitable to be further developed for human medicine, there is a huge demand for innovate technologies. Novel vaccines to fight WNV were developed as part of the EU-funded WINGS (West Nile Integrated Shield Project) project, which is coordinated by the Fraunhofer IZI Vaccine Technologies unit. They are based on recombinantly manufactured proteins and on DNA plasmids, which encode a WNV antigen. DNA vaccines trigger the natural production of antigens in the body of an inoculated person, which in principle works like a viral infection, but is completely harmless. Nevertheless, this leads to a profound stimulation of the immune system. In the WINGS project, this type of DNA plasmid was used as a combination vaccine with a recombinant protein. This strategy, and also the recombinant protein alone in combination with a new type of adjuvant, led to full, long-lasting protection against a WNV infection in various animal models. This protection was maintained against a series of genetic variants of the virus. This is crucial, especially in Europe, where several different forms of WNV are circulating, often in the same geographic areas. Following this highly successful preclinical development, the next stage – clinical testing on humans – is now being prepared.

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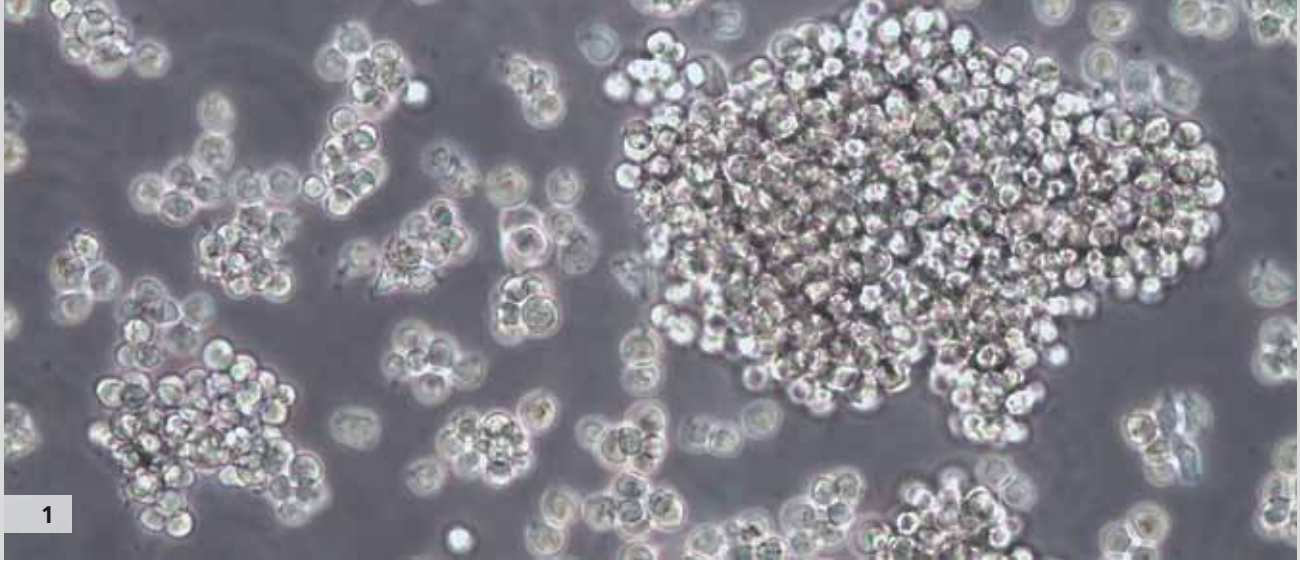
SEVENTH FRAMEWORK PROGRAMME

West Nile Shield Project WINGS

1 *Schematic structure of the West Nile Virus*



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Prevention of immunological complications using epitope-specific antibodies following hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) aims to permanently regenerate healthy, functional hematopoiesis and to heal underlying malignant diseases (e. g. leukemia) in patients. Over 60,000 HSCTs are carried out every year around the world – a figure which is on the rise. Despite considerable advances in the field, many patients may still fall ill as a result of the procedure's main complication: Graft versus Host Disease (GvHD). Drugs used at present lead to the entire immune system becoming suppressed, which is associated with an increased risk of infection, secondary tumors, or a risk of the underlying illness returning.

This is why investigations into a new immunomodulating therapy using epitope-specific anti-human CD4 antibodies forms the focus of the project with regard to the prevention of GvHD and its impact on tumor development. A murine leukemia stem cell transplantation model was developed for this purpose using mastocytoma cells and transgenic mice which display CD4 and HLA-DR. It facilitates the testing of epitope-specific anti-human CD4 antibodies directly in the mouse model.

The investigations showed that the anti-CD4 antibody treatment was able to successfully prevent GvHD. It also maintained the Graft-versus-Leukemia (GvL) effect of the transplant without experiencing a negative impact. Further experiments using human leukemia cells in a NSG/SCID mouse model are intended to verify these results. Should the experiments prove to be successful, the therapy procedure shall be applied in a clinical trial. Treatment of this kind, which disables GvHD while maintaining the GvL effect, would make HSCT safer and applicable to other indications (e. g. autoimmune diseases).

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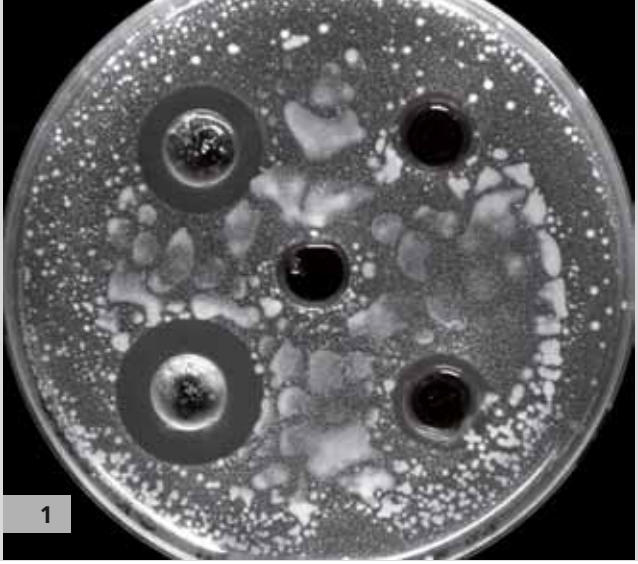
1 *Mastocytoma cell line P815 (20x)*



1

Development of therapeutically effective peptides for the treatment of contagious diseases in the field of dentistry

The need for new antibiotic drugs based on bioactive substances has risen greatly in recent years due to the increased resistance of human pathogenic germs. Strong growth is also predicted for the future of this segment. In the Vascular Biology unit, antimicrobial peptides are being developed to fight multiresistant hospital germs and oral, human pathogenic germs, aided by a specially established technology platform. This DNA-based technology facilitates the development of an appropriate, antibiotic peptide against, in principle, every type of hospital germ by using a high-throughput technique. Some of these antimicrobial peptides have a broad-spectrum effect and could thus be applied against a number of different types of bacteria or even pathogenic fungi (e. g. candida albicans). Over the course of the past five years, more than ten sequence libraries were established with partly differing ranges of efficacy, e. g. against human-pathogenic oral germs (cariogenic germs such as streptococcus mutans, streptococcus sobrinus or pathogens associated with periodontitis such as actinobacillus actinomycetemcomitans or porphyromonas gingivalis), germs found in the gastrointestinal tract (heliobacter pylori) and also against germs found in the respiratory tract (hemophilus influenzae).

Emphasis is currently being placed on developing antimicrobial peptides against periodontitis and/or caries pathogens. Although the incidence for caries has decreased thanks to improved prophylaxis, oral hygiene and the extensive availability of fluorinated drinking water, contagious diseases in the field of oral health cost Germany billions of euros every year.

In 2013, among other things, two antimicrobial peptides were developed in the Vascular Biology unit which are extremely selective in destroying the two most significant caries pathogens (streptococcus mutans and streptococcus sobrinus), but do not negatively impair human microbiome, which is important for the integrity of the oral cavity. Besides this, these peptides did not have a negative effect on epithelial cells, which means they can be used in the areas of restorative treatment, caries prophylaxis and dental implantology. On the surface of teeth it could also be demonstrated that both peptides clearly delay biofilms from forming, which prompts its further use in dental hygiene products (mouthwash, toothpaste). The structure of other peptides render them chemically inert to reactive oxygen. This makes them optimally suited to be used, for example, as another additive in ozone-based periodontitis treatments. Initial applications of antimicrobial peptides are planned to begin in the field of dentistry as of 2014.

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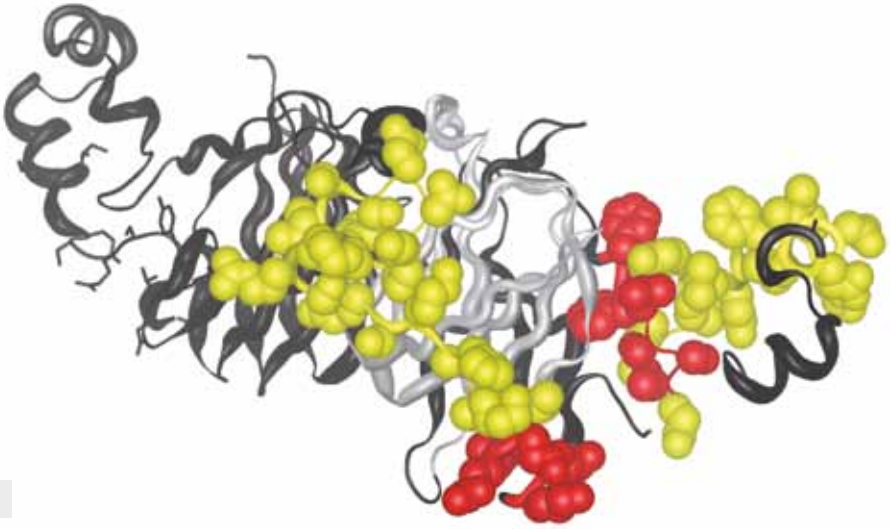
1 *Agar diffusion test to determine the antibacterial efficacy of peptides*



1

Mapping the human immune response

Being able to gather all the information regarding a patient's antibodies, and thus recent diseases, vaccinations, etc., in just one step appears to be a rather impossible feat. New peptide phage display libraries bring us a little closer to achieving this goal: they surpass any previously developed, comparable libraries due to their novel synthesis methods for the applied peptide genes. One of the projects benefiting from this technology is the 'MAVO' LowAllergen project, funded by the Fraunhofer-Gesellschaft.

We have used the example of soy allergies to identify the molecular structures within the allergen that may trigger the allergy, in this case soy proteins. In collaboration with the Fraunhofer IME, these epitopes are identified using classic procedures and the new phage display procedure. The Fraunhofer IZI's Cell Engineering/GLP unit manufactures antibodies for detection in food; the Fraunhofer IVV in Freising, which is coordinating the project, then applies this knowledge to create processes to produce hypoallergenic soy protein.

The dermatology unit at the University Hospital of Leipzig first collects and also characterizes serums from allergy sufferers. These serums are characterized further at the Fraunhofer IZI, for example with the aid of purified proteins. We can use these serums, without further purification, in order to select peptide phages from the new libraries. All the millions of bound phage particles are sequenced using next generation sequencing, thus providing information on each potentially binding peptide. By drawing comparisons with the established proteins in the soy beans, potential epitopes can be identified, which in our case concerns the significance of each individual amino acid within a protein which is recognized by the patient's antibodies. Finally, the findings are validated using synthetic peptides and all patient serums are then tested for the presence of suitable antibodies.

This procedure is extremely sensitive as, in theory, a single antibody molecule in the selection procedure is all that is required to identify this type of epitope by binding to a peptide-carrying phage particle. Based on our present results, by the end of the project we expect to have identified over twice as many epitopes than the number previously identified over decades using traditional research methods.

Most notably, the previous methods can only approximately determine which amino acids really interact with the antibodies. Using the new procedure developed by the Fraunhofer IZI, individual amino acids can be identified instead. The figure above depicts a comparison between what is known from the literature and the discovered amino acids.

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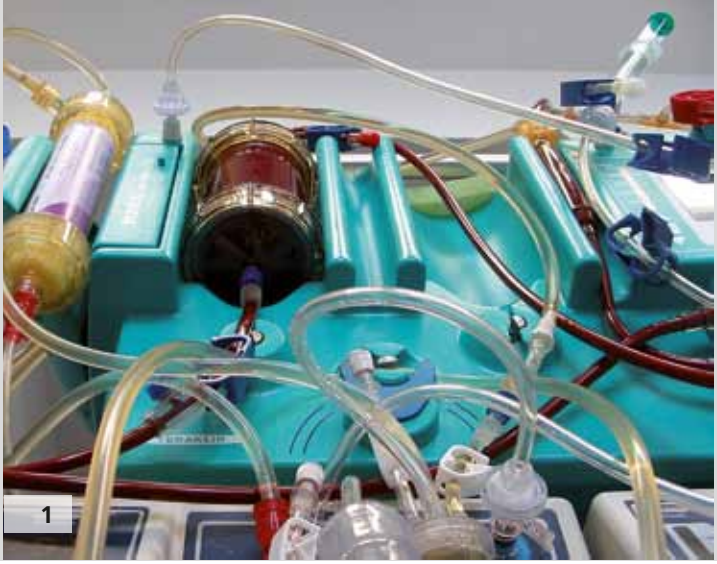
1 *A structure of the alpha subunit of the soya protein beta-conglycinin with two epitopes from the literature in yellow and what are arguably the only relevant amino acids in red*



1

Characterization of the body's natural albumin function as a diagnostic and therapeutic approach in acute liver failure and other diseases

Albumin is a water-soluble protein produced naturally in the body. In the human organism, albumin plays a vital role in regulating water balance. Besides this, the protein facilitates the transport of water-insoluble substances. This ensures that organs are provided with nutrients and that metabolic end products are transported away to the excretory organ. The function of albumin is also relevant for the transport of drugs.

In the case of many diseases, albumin transport and the associated excretory function sometimes becomes restricted, for example in the case of hepatic and renal diseases or multiple organ failure in patients on the intensive care unit. Clinical trials were able to demonstrate that albumin function diminishes as the severity of the disease increases. This results in toxic metabolic products accumulating in the body.

Improved albumin function achieved by means of suitable therapeutic procedures, such as albumin dialysis, increases the chance of survival, especially in critical patients. To be able to use appropriate types of therapy early enough, reliable diagnosis procedures are required in order to precisely assess a patient's condition. A test system developed by our institute allows the transport function of albumin to be characterized. In doing this, the unbound portion of a marker is determined in a sample. Quantitative assertions may be made by comparing this with the unbound portion of a reference albumin in the same concentration. The test system is offered as a part of our service portfolio.

This new diagnostic procedure is expected to have a significant influence on the future treatment of diseases. Besides assessing the severity of the disease and providing a prognosis, it is also intended to provide support when selecting the right treatment for the respective patient (albumin dialysis or albumin infusions) and to prevent overdosing.

Furthermore, the procedure is to be used as a target parameter in clinical trials in order to characterize and compare the repercussions of various therapeutic possibilities.

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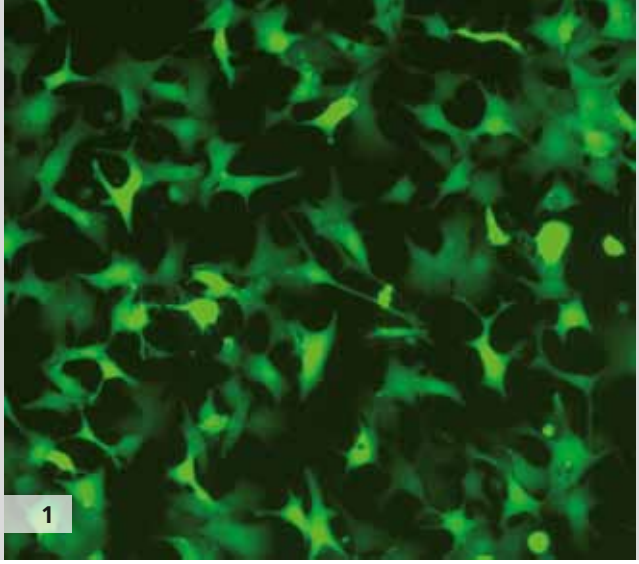
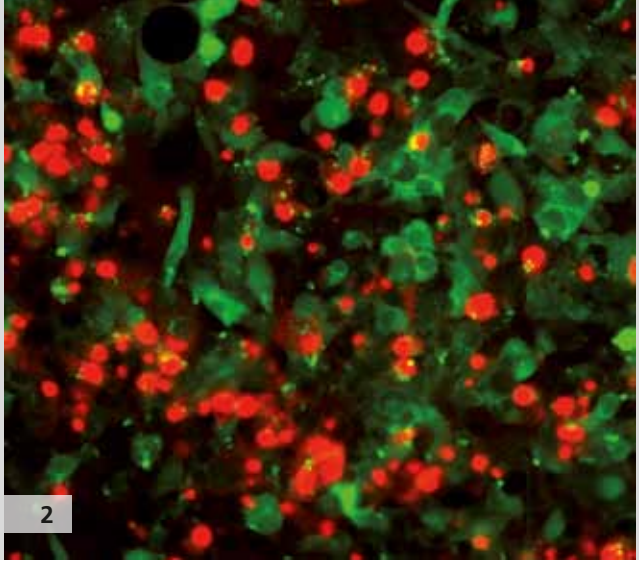
1 *Measuring albumin function supports the clinical control of albumin dialysis.*





Biosensor technology for prevention or early detection of liver failure

Liver failure and liver dysfunction are serious conditions associated with a high risk of death. Liver failure can be caused by primary acute liver disease or the acute worsening of a pre-existing liver disease. In addition, drugs such as paracetamol also have the potential to cause acute liver failure. Hepatotoxicity is the most frequent side effect of drugs and the main reason for retracting already approved medicines from the market. More than 20 % of patients who suffer from multi-organ failure caused by inflammatory disease syndromes, e. g. sepsis, experience liver dysfunctions or even advanced liver failure.

At present there is no reliable test for the early detection of liver failure. Moreover, most drugs are not extensively and specifically tested for their hepatotoxic potential. We therefore developed a micro titer plate assay using human liver cells (hepatocytes) which can be used to detect liver failure at an early stage in the clinic and to evaluate the toxicity of drugs and medical devices. We are working on this project in close cooperation with the Clinic and Polyclinic for Anesthesiology and Intensive Therapy at the University Hospital of Rostock.

Human hepatocytes are very sensitive in their reaction to inflammatory and toxic stimuli. In this respect, experimental cells react with reduced vitality and synthesis capacity as well as with alterations in the P450 enzyme system. Optimizing and standardizing the procedure allows us to make reliable statements on exogenous and also endogenous toxicity. Eventually the use of cell-based diagnostics with permanent cell lines may also be able to greatly reduce the necessity for animal experimentation. Besides ethical considerations, this is also an important aspect in reducing costs. In several studies we were able to detect candidates which demonstrated significant hepatotoxic potential in medicines which are relevant for patients in intensive care units, e. g. muscle relaxants and antimycotica. In order to validate the use of the biosensor test system for the early detection of liver failure, we have so far conducted three clinical trials and obtained very promising results. In addition, the biosensor technology for the prevention or early detection of liver failure is offered as part of our services portfolio. The biosensor is patent protected in Germany and Europe and is planned to be further developed as a product in future as a micro titer plate assay for early detection.

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1 *Live/Dead staining: HepG2/C3A – medium control (green fluorescent (vital) cells)*
2 *Live/Dead staining: HepG2/C3A with 7.62 mM paracetamol (increase in red fluorescent (dead) cells)*

DEPARTMENT OF CELL THERAPY

Core competencies of the department

- Isolation, expansion and differentiation of (stem) cells
- Infarction models (focus on brain and heart)
- Models of chronic brain ischemias and neurodegenerative diseases
- Experimental imaging (including MRI, BLI, and confocal microscopy)
- Experimental neurosurgical techniques including stereotaxic surgery
- Preclinical study design and quality assurance
- Processing fundamental neuroimmunological issues
- Viral and non-viral generation of iPS cells (human and murine)
- Histology and Immunohistochemistry
- Multi parametric flow cytometry of organ lysates
- T-cell infiltration patterns in vitro/in vivo
- Evaluation of tumor immunological parameters

A selection of products and services offered by the department can be found on page 67.

IN CONVERSATION WITH DR. DR. JOHANNES BOLTZE

You worked at the Harvard Medical School in Boston between October 2012 and October 2013. What did you learn from this experience and how, if at all, has it affected your work in the department? Besides the valuable contacts and wealth of cultural impressions that I was able to establish and collect in New England, I was especially impressed by the work climate. It is much more performance-based than in Germany: outstanding academic performance is indeed also practically associated with automatic advancement in the academic system and clear remuneration benefits. I was also impressed that many aspects of job profiles for experienced scientists and unit heads in Harvard are very similar to, and sometimes even more demanding than, those expected of the members of staff working for the Fraunhofer-Gesellschaft. This includes the need to independently finance one's equipment and job, which always comes in the form of a temporary contract, and to always, of course, perform to the best of one's scientific ability. Excellent contributions to fundamental science, without doubt, form the basis of extensive industry cooperation projects and act as an "acquisition instrument" for such projects. What was also surprising for me was the fact that both the infrastructure and the standard of our colleagues' education are not only fully competitive, but are also clearly superior in a number of areas. By adopting a combination of the best and most practical approaches from both spheres, I am therefore convinced that we will be able to significantly expand our productive capacities even further not only in the area of application-oriented industry cooperations, but also and more specifically in the area of fundamental science. Implementing and translating what I learned at Harvard will form a basis for the activities that will help structure our department in coming years.

What are the key research themes in the department and what strategic orientation will you pursue in the coming years? The work in our department remains focused on cell-therapeutic and diagnostic procedures for neuro-degenerative diseases and on the field of applied stem cell technology. Alongside the field of chronic ischemia, we will significantly expand our expertise in future towards the area of neuroimmunological issues. We also intend to push on with the development of our own products, particularly in the area of diagnostic procedures and applied cell technologies, and gradually build up the clinical expertise among our members of staff. This should make new types of successful industry cooperations accessible to the department and could even form the focus of our work in the long term, rather than us concentrating solely on the development of cell therapeutic procedures. Moreover, we will continue to educate and train young scientists and our technical members of staff – an initiative which is also set become much more significant across the institute.

In 2014, the department will organize the 8th International Symposium on Neuroprotection and Neurorepair. What do you expect to come out of the event? We expect nothing less than for the 8th ISN&N to be the largest event in the series to date. Once again, the program comprises a number of highly interesting contributions from the fields of neurological basic research, clinical translation, and technical innovations on the part of industry. We have managed to bring over 30 internationally renowned colleagues to Magdeburg as speakers. Furthermore, we will set the course for the future of the event series at the Magdeburg event as its main organizers, Professor Klaus Reymann and Professor Georg Reiser, are unfortunately only able to support us in the capacity of emeriti as of 2015. The fact that the world's largest initiative for quality-optimized and global stroke research, the MULTIPART consortium, has arranged to hold its annual meeting within the periphery of our event has also given us a great deal of motivation.

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UNITS

Experimental Imaging Unit

Experimental imaging stands at the interface between engineering and life sciences. It supports research activities which require the acquisition and processing of imaging and involves various technical devices and software. Due to constantly evolving methods in the applied procedures, the unit is constantly adapting its field of work to the latest developments. Its main function is to apply current imaging methods to the tasks required by project partners.

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Immunotherapy – Oncology Unit

The unit encompasses two major areas of interest. New strategies for treating cancerous diseases are developed and tested with the aid of innovative tumor models. The unit also focuses on optimizing therapeutic cancer vaccines, e.g. through different administration strategies, in view of the fact that tumor immunology and re-engineering of the immune system show promising results compared with current types of treatment.

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Ischemia Research Unit

The common conditions stroke, myocardial infarction and vascular dementia are caused by an acute or chronic lack of supply of blood and oxygen. This ischemic tissue damage results in an inflammatory response which is important for the healing process, but may also exacerbate the initial damage. Comorbidities such as hypertension, hyperlipidemia and chronic inflammation especially determine the relationship between protective and damaging influences. The unit explores the foundations of these correlations with the aim of identifying and preclinically validating novel therapy options.

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Clinic-oriented Therapy Assessment Unit

The unit tests and develops innovative diagnosis and therapy procedures for stroke. As the possibility of being able to transfer findings from small-animal models to human patients is sometimes only very limited, a globally unique, large-animal model was established for the translational approach. Using this model means that tests can be carried out under conditions which come close to patient treatment in a clinical setting. Both the gyrencephalic brain structure and the size of the brain in the human situation are much more similar in the sheep model than they are in the small animal.

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Cognitive Genetics Unit

The Cognitive Genetics unit investigates the foundations and application possibilities for the genetics involved in cognitive processes. The main focus of our work is on the genetics of dyslexia. Our main aim is to develop an early screening test which will effectively facilitate the functional regeneration of dyslexia-related cellular deficits in the future.

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Stem Cell Biology Unit

The unit combines insights from stem cell and gerontology research to develop novel strategies for tissue regeneration. We pursue different innovative approaches to "rejuvenate" adult stem cells in vitro and/or in vivo, so that these cells can resume their function as promoters of regeneration, particularly in older patients.

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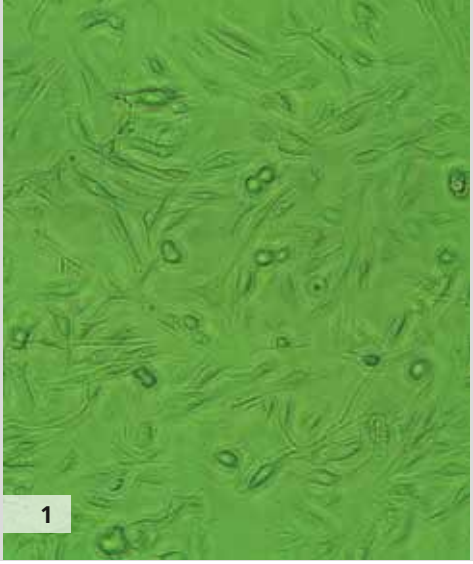

1

PROJECT EXAMPLES

Development of immunotherapies for oncology

Therapeutic DNA cancer vaccines present a key alternative to traditional methods in the field of tumor immunotherapy. These DNA vaccines show a relatively stable in vitro expression and a distinct immunological response in patients. Since the efficacy of this response, however, is triggered by the application technique, optimizing this can further enhance immunotherapies. These application techniques include physical, biological and non-biological procedures which have not yet all been tested in clinical studies. Major issues involved in the application of DNA cancer vaccines include low antigen expression, inefficient cellular migration of the plasmids and the insufficient stimulation of the natural immune system.

Despite progress having been made with regard to application techniques for cancer vaccines, and although the immunogenicity of the vaccines has improved, leading to a robust immune response, the immunological resistance of the tumor continues to be limited. It is known that tumor cells react differently to this specific type of T-cell resistance. Jonathan Bramson from McMaster University has developed a high-throughput procedure to identify new components that can make tumor cells more sensitive to cytotoxic T cells. We propose to use the McMaster high-throughput technology together with the peptide libraries developed at the Fraunhofer IZI to identify novel bioactive peptides for the sensitization of tumor cells. Such peptides may demonstrate tumoricidal and indeed T-cell activating characteristics that may lead to enhanced tumor lysis. Positive outcomes of this procedure could be useful adjuvants for immunotherapy.

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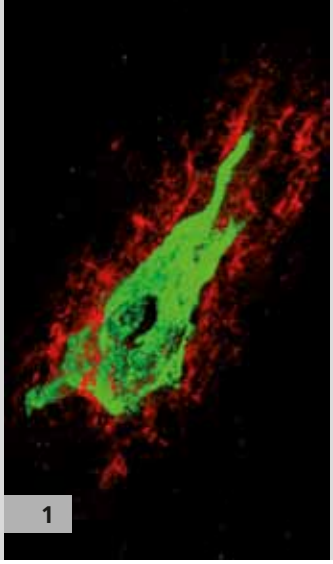
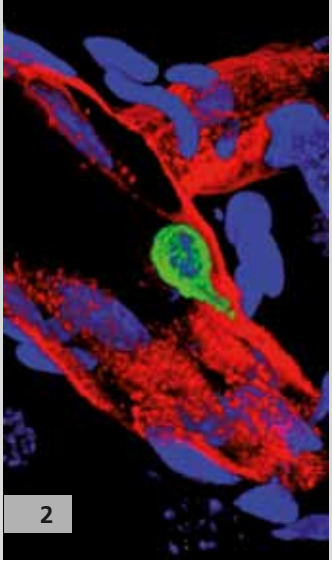
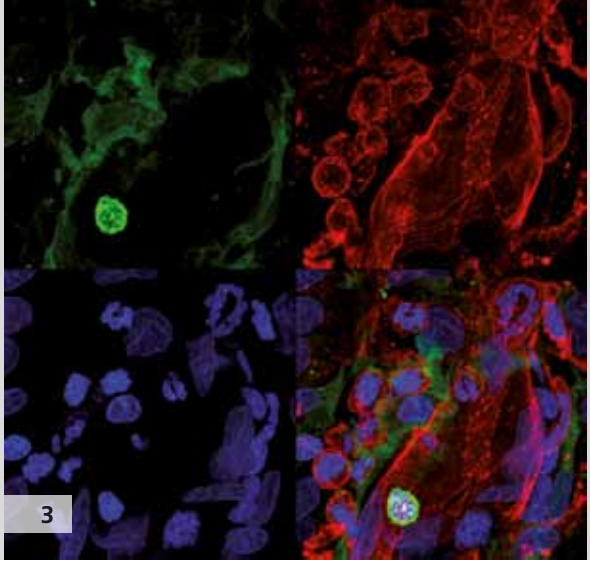
1 *Tumor cells under the microscope*







Treatment of chronic vascular inflammation in diseasecerebral microangiopathy

Cerebral microangiopathy counts among the most common neurological diseases. Typical vascular risk factors, such as increased blood pressure, age and diabetes mellitus, lead to an advancing loss of function in the small cerebral blood vessels (arteriolosclerosis). Consequences include a chronic lack of supply to the brain tissue as well as minor and severe brain hemorrhage. Patients suffer from an insidious degeneration of cognitive performance through to severe dementia and from ischemic or hemorrhagic strokes.

Major cross-sectional studies show that when vascular risk factors are present, corresponding changes in the brain can already be detected in middle-aged individuals and lead to the brain aging prematurely by up to ten years.

Cerebral microangiopathy is an underestimated condition as it initially progresses with very few symptoms yet it is associated with serious secondary diseases such as stroke. Deteriorating cognitive performance in older age, in contrast, is often misunderstood as an unavoidable, age-typical transformation. In actual fact, cerebral microangiopathy is a chronic disease which leads to progressive damage to the brain over years and decades. One significant disease mechanism appears to be the inflammation of the vascular wall, which in the long term leads to a transformation in blood flow properties and to the infiltration of inflammatory cells. Interrupting this inflammatory response might represent a causal therapeutic approach for cerebral microangiopathy.

The principle aim of this project is the preclinical exploration of the immunological disease mechanisms of cerebral microangiopathy. Using laboratory animals which demonstrated arterial hypertension, the unit was able to detect changes in vascular wall cells in specific regions of the brain, which may depict an early stage of the disease. A second, also preclinical phase will investigate the efficacy of immunomodulating substances on the symptoms of cerebral microangiopathy.

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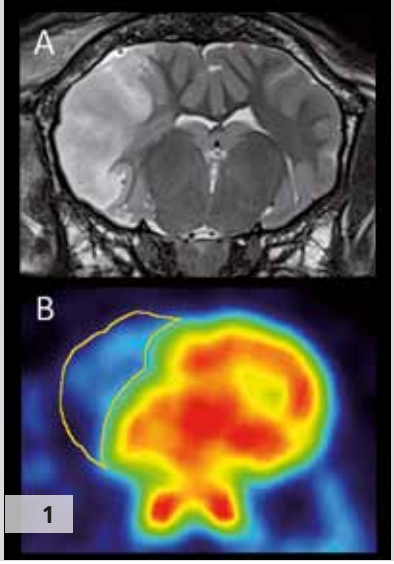
1 *Dysfunction of the blood-brain barrier*
2 *T lymphocyte (green) migrating through vascular wall (red)*
3 *T lymphocyte (green) and macrophages (red) in inflammatory CNS lesion*



Therapeutic impact of targeted transcranial neurovascular stimulation

The human brain needs a blood supply (cerebral blood flow, CBF) of 80 ml/100 g brain tissue and minute. If blood flow in circumscribed brain areas is seriously impaired, massive functional and tissue loss can occur there, resulting in a stroke. Brain areas which are completely cut off from a blood and thus a nutrient supply mortify very quickly. The affected brain tissue can, however, be rescued from dying off if the CBF is restored immediately. Hence, a rapid and sustained recovery of the CBF is crucial in bringing about as lasting an improvement as possible in affected patients. Due to time restrictions (a timeframe of 4.5 hours) and contraindications associated with treatment options available at present which involve reopening the vessel, less than 5 % of all patients currently benefit from this procedure.

The medical technology company Nervive and the Fraunhofer IZI are investigating a way of improving this situation by means of a new therapy concept. This concept is based on a technique that can influence the blood flow in the brain by using magnetic fields. So-called Transcranial Magnetic Stimulation (TMS) can increase the circulation in defined brain areas by stimulating a cranial nerve in the inner ear region, thus limiting the damage caused by the stroke.

The safety and efficacy of the procedure is to be verified using highly diagnostic model systems. In doing so, among other things, special imaging procedures are performed in cooperation with Leipzig University Hospital in order to obtain a location-specific description of the CBF. On the basis of these investigations, the TMS technique can be optimized accordingly and the development of a prototype for use in practice can be driven forward.

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Europa fördert Sachsen.
EFRE
Europäischer Fonds für regionale Entwicklung

1 *A) MRI image of acute stroke in the left cerebral hemisphere of a sheep*
B) Depiction of cerebral blood flow using positron emission tomography; a clear reduction in blood flow can be seen in the left cerebral hemisphere.

1

2

3

LEGASCREEN – development of a multi-modal early screening test for diagnosing dyslexia

Dyslexia is a severe disorder in acquiring reading and writing skills, affecting about 5 % of all German schoolchildren. It is one of the most common developmental disorders in childhood and youth. Dyslexia is unrelated to the child's intelligence. It results in tremendous problems in school, education, and at work.

One of the main problems hampering successful therapy is late diagnosis: with the current methods, dyslexia cannot be reliably diagnosed until the end of the 2nd grade. By this time, a large part of speech-development has, however, already taken place, and a lot of precious time for providing support and therapy is inevitably lost.

Our project, a joint venture between the Fraunhofer-Gesellschaft and the Max Planck Society, is based on our previous research into the genetics of dyslexia. The earlier a disposition towards dyslexia can be recognized in a child, the more likely it is that this disorder can be counteracted by providing a targeted form of language support, and the greater the chance of reducing any problems. To do this, different research approaches are combined: genetics together with specific brain activity measurements (EEG).

Dyslexia is inherited in 50 % to 70 % of cases. Genetic material (DNA) practically stays the same during a person's life span. Consequently, respective genetic risk variants can already be used for diagnostic purposes at an early stage, irrelevant of whether or not the child is yet able to read and write. As a starting point, our project will utilize and optimize known genetic variants which contribute to the development of dyslexia.

The other key part of our test is based on electroencephalography (EEG) – a procedure which allows brain activity to be measured without demanding the attention of the child. Research has shown that children who go on to develop dyslexia already demonstrate distinctive features in brain activity at an early age in response to specific language stimuli.

Magnetic resonance imaging (MRI), which is also involved in our study, is used as a link between genetics and EEG. It allows us to better understand structural features in the brain, however it will not form part of the test procedure which is to be developed.

To summarize, the aim of this project is to develop an early screening test for dyslexia which recognizes the respective disposition towards dyslexia long before this can be seen using conventional testing methods. We believe that, in future, this type of early testing will significantly improve access to dyslexia therapy at an early stage in the child's development.

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1 *Our aim: taking pleasure in successful learning*
2 *EEG examination*
3 *MRT examination*

1

Induced pluripotent stem cells from mRNA reprogrammed cells

Modern medicine has its hopes pinned on stem cells. Here it is predominantly the fact that stem cells are able to develop into as many different types of cell and tissue as possible that is of particular interest to medical research. Until now, embryonic stem cells were therefore viewed as the most promising resource for pluripotent stem cells. Embryonic stem cells are capable of developing into any type of body cell and also have an extremely high capacity to divide. In order to obtain embryonic stem cells, however, blastocyst stage embryos have to be destroyed, which is why this research is, in itself, extremely controversial with regards to ethics. Work involving embryonic stem cells is regulated to variable degrees in the countries belonging to the European Union. Particularly strict regulations apply in Germany. In October 2011, a landmark decision was made by the European Court of Justice which prohibited the patenting and commercialization of human embryonic stem cells and procedures used to obtain such cells.

The ethical dispute and the given conditions call for an alternative in order to keep up with international research and medical advancement. Induced pluripotent stem cells (iPS) are very similar to embryonic stem cells in terms of their capabilities and characteristics. By means of a so-called reprogramming of somatic cells, a state is achieved which allows the iPS to be differentiated into nearly every type of cell. Most ways of manufacturing iPS, however, use viruses or viral factors, thus excluding medical application.

At the Fraunhofer IZI, a reprogramming method has been developed which is based on mRNA and does not involve permanent changes in the genome. Thus, iPS can now be manufactured with a high level of medical potential. Patient-specific stem cells may be used to cultivate tissue for regenerative therapies. Initial applications are, however, also conceivable in the areas of pharmacological development and toxicology.

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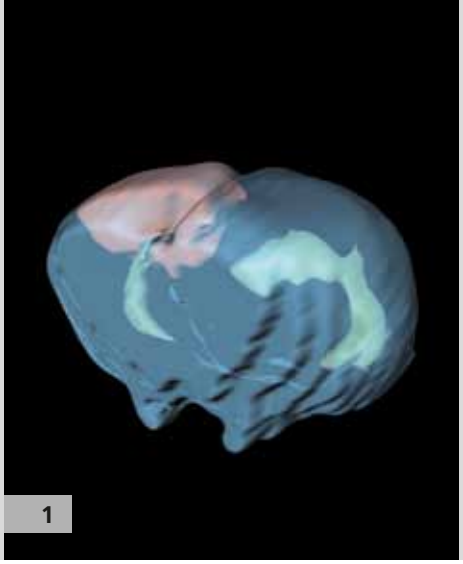
1 *Human iPS cells which were differentiated into neurons*



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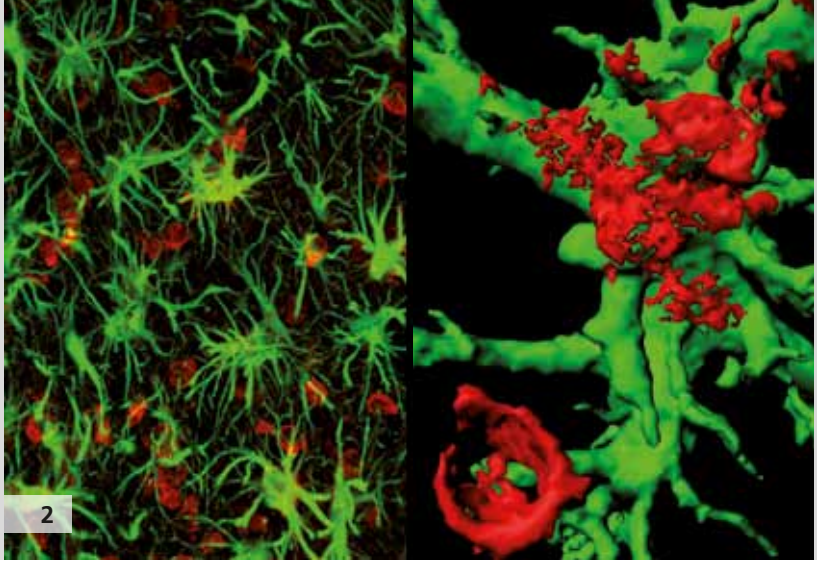

2

Use of 3D rendering in modern imaging procedures

The field of life sciences presents us with a variety of diagnostic options. Procedures applied in this field use the entire span of the electromagnetic spectrum, ranging from short-wave roentgen radiation (computer tomography) and light which is visible to humans (microscopy) right over to high frequency magnetic resonance imaging. Each one of these procedures visually illustrates very specific structures relating to biological processes in the living organism. Thanks to the increased resolution of the devices, sufficient data can now be gathered to create a virtual reproduction of the examined structures. Calculations can be made and biological processes visualized based on the rendered computer models. This is made possible due to the use of sophisticated computer systems and special software applications.

Pathological processes which emerge, for example, in the case of the widespread condition stroke, can thus be precisely quantified. It is not possible to depict the affected structures directly as they are shielded in the cranium. With the aid of MRI scanners with extremely high field strengths (up to 140,000 times the strength of the earth's magnetic field) and special algorithms which are used to segment these structures, the damaged region can be depicted "in vivo" without the need for surgery. By using different contrast methods, macroscopic pathologies are made visible on the screen as 3D objects (image 1).

Far-reaching microscopic reconstruction processes take place in the affected areas of the brain following brain tissue damage caused by trauma or hypoxia, which cannot be seen using MRI scanners. The brain's connective and supportive tissue (glial cells) reacts to this by enlarging the cells (hypertrophy) and increasing the number of cells (hyperplasia). In order to be able to depict regeneration, the affected region is immunohistochemically stained and scanned using a confocal laser scanning microscope. The resulting data record is processed and transformed into a 3D structure. This makes it possible to precisely describe the number of cells, their morphology, their interaction with other cells, and their changes over the course of time (image 2).

Both processes facilitate a quantification of pathological changes following brain damage and are therefore suitable for verifying the efficacy of new therapeutic procedures. The algorithms used to segment, evaluate and assure quality are hugely similar here in spite of the different methods. Pooling these competences into one unit thus facilitates various synergies.

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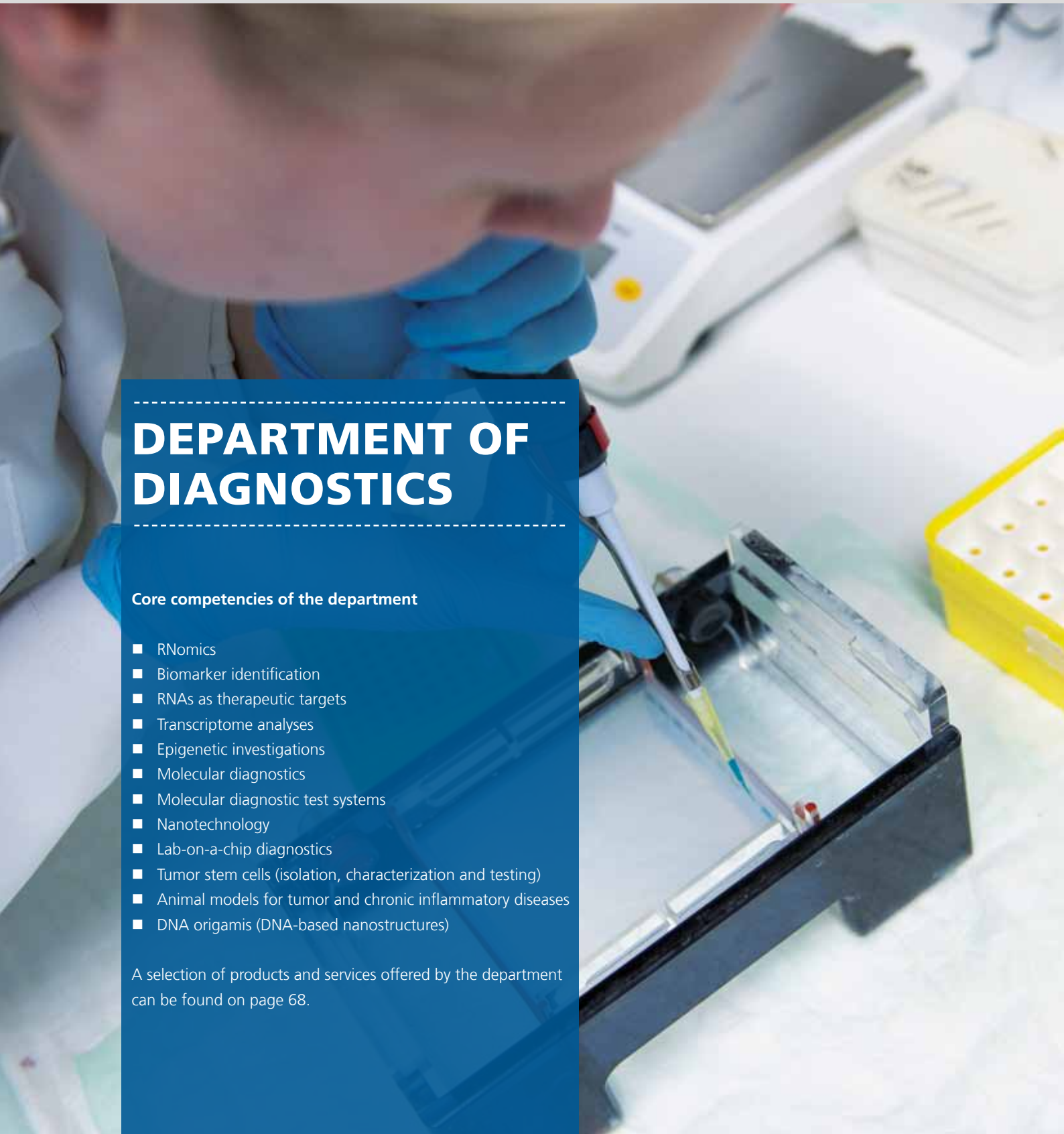
1 *Visualization of a stroke in a 3D model of a rat's brain*
2 *3D model of astrocytes based on immunohistochemical staining*



DEPARTMENT OF DIAGNOSTICS

Core competencies of the department

- RNomics
- Biomarker identification
- RNAs as therapeutic targets
- Transcriptome analyses
- Epigenetic investigations
- Molecular diagnostics
- Molecular diagnostic test systems
- Nanotechnology
- Lab-on-a-chip diagnostics
- Tumor stem cells (isolation, characterization and testing)
- Animal models for tumor and chronic inflammatory diseases
- DNA origamis (DNA-based nanostructures)

A selection of products and services offered by the department can be found on page 68.

IN CONVERSATION WITH PROF. DR. FRIEDEMANN HORN

The joint project RIBOLUTION, which you have been coordinating since 2011, is nearly completed. How would you summarize the key findings and which clinical and commercial applications are now conceivable? In the RIBOLUTION consortium (Innovative Ribonucleic acid-based Diagnostic Solutions for Personalized Medicine), funded by the Fraunhofer Future Foundation, clinical samples for prostate cancer and chronic-obstructive pulmonary disease (COPD) were used to identify new biomarkers for the diagnosis and prognosis of these diseases. By genome-wide next-generation sequencing of all RNA molecules present in these samples, promising novel biomarker candidates were discovered. For prostate carcinoma in particular, we identified biomarkers that were significantly superior to those used for current diagnostic assays. Hence, these biomarkers possess excellent market potential. Specificity and sensitivity of the novel markers could be validated using other analysis techniques. For 42 of these biomarkers, patents were filed in 2013, and additional patent applications are currently being prepared. RIBOLUTION also started a partnership with the PROGRESS network ("Pneumonia Research Network on Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis"), which is funded by the German Federal Ministry of Education and Research (BMBF). The network looks for new ways of diagnosing sepsis. Over 800 patient samples have already been processed and are currently being analyzed. With the help of the discovered biomarkers, we hope to improve diagnostic methods for these diseases – something which is urgently required in the clinic.

Last year, the department was expanded to include nanotechnology expertise. How has the DNA origami technology integrated into the department's service portfolio? The DNA Nanodevices unit led by Dr. David Smith is seizing the unique opportunity to design the base sequences of DNA molecules in such a way that, by self-assembling, they form two or three-dimensional structures. These structures can be used in a number of different ways, for instance in clinical diagnostics through the development of minuscule biosensors or nanocircuitry, or in therapeutics for the specific delivery of molecules to target cells in vivo and in vitro. This opens up a huge spectrum of novel medical applications.

What achievements are you particularly proud of in the department and what are your goals for the coming year? Within the past two years, we were able to attract and start a number of new projects that are carried out jointly with industry partners. This proves how attractive the department's expertise and areas of research are to the industry. Therefore, we feel encouraged to continue down this route and will extend and further strengthen our portfolio by additional innovative technologies and research offers.

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UNITS

Inflammation Models and Immunodiagnostics Unit

This unit develops rapid, straightforward, immunological, cell biological and genetic analysis and model systems for the areas of graft rejection, inflammation research and tumor biology, in particular for joint and pulmonary diseases. This involves the use of innovative immunoassays, genetic analyses, complex cell culture models and animal experimental approaches.

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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 bio-chips, 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. The unit has been funded by the Fraunhofer-Gesellschaft's Attract program since 2013.

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Nanotechnology Unit

This unit works on the development of molecular diagnostic test systems for the food and medicine/clinical practice sectors. The unit focuses on the development of test-strip based rapid tests to detect infecting agents, bioanalytical sample preparation and the application of nucleic acid-binding proteins. Two novel lab-on-a-chip diagnostic platforms, e. g. based on functionalized magnetic particles, were developed in order to quickly analyze patient samples.

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RNomics Unit

The RNomics unit identifies and characterizes disease-associated non-protein-coding RNAs (ncRNAs) for the development of novel diagnostic markers and therapeutic targets. The methods and strategies required for this task are developed by the unit, paying particular attention to their general, disease and system-independent applicability.

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Tumor Stem Cell Unit

This unit's objective is to develop therapeutic strategies based on cells and agents for the treatment of neoplastic diseases based on the elimination or modification of tumor stem cells (TSCs) in the relevant malignant tumor. This concept is to be used to describe the TSCs of further tumor entities and to facilitate therapeutic innovations in the field of internal oncology.

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1

PROJECT EXAMPLES

Influence of a tea extract on the function of myeloperoxidase in a chronic rat model of rheumatoid arthritis

About 1 % of the world's population suffers from rheumatoid arthritis (RA), which is considered to be the most common form of chronic inflammatory joint disease. The principal characteristics of RA are cartilage destruction, joint swelling and bone erosion. The immunological response and inflammatory events occur in phases, which foster the disease. In these periods, patients suffer most from the previously mentioned symptoms. The currently available pharmacological therapy mainly consists of nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) and other biologics. All of these therapeutic agents may well suppress the inflammation and relieve pain but, to date, a complete remission using these means has not been possible.

At the beginning of an acute inflammation, immune cells are recruited and activated. One of the first cell types in this reaction are the polymorphonuclear leukocytes (PMNs). They mediate defense against pathogens and are involved in the progression of inflammation by releasing various cytokines. A regulating factor within these processes is the heme-containing enzyme myeloperoxidase (MPO), which is found predominantly in PMNs. The catalytic activity of MPO leads to the release of hypoclorous acids (HOCl), which is a critical factor in terminating inflammatory events. This has given rise to the hypothesis that reduced MPO activity leads to RA becoming more chronic.

This has prompted us to analyze the role of MPO in a chronic model of pristane-induced arthritis in a small-animal model (rat). We will modify the enzymatic activity of MPO by applying a component of green tea extract, namely epigallocatechin gallate (EGCG), and compare the effect with that of the current gold standard, methotrexate (MTX).

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1 *Green tea extracts are being investigated regarding their efficacy to treat rheumatoid arthritis.*

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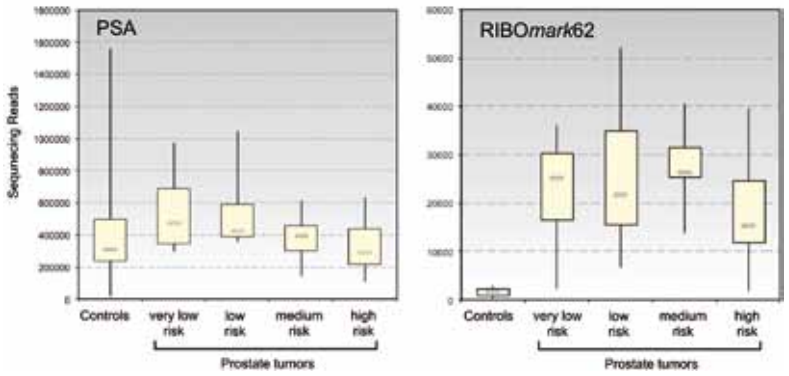

2

RIBOLUTION – integrated platform to identify and validate innovative RNA-based biomarkers for personalized medicine

Complex diseases represent a particular challenge for medicine and health systems. In light of the current demographic trend, the incidence of oncological, chronic-inflammatory, and degenerative diseases is steadily rising. Personalized medicine promises to provide an individually optimized therapy, based on the exact type of disease and the individual patient's response to the treatment available. This, however, requires precise diagnostic means, i. e. biomarkers that allow disease type and progression to be determined and therapy response to be predicted. The clinical need for new biomarkers is therefore constantly rising. The joint project RIBOLUTION, which is funded by the Fraunhofer Future Foundation and coordinated by Fraunhofer IZI, aims to develop such new biomarkers. We have established an efficient process of screening and validating new biomarkers from the ribonucleic acid (RNA) molecule category, and have applied this process to various diseases. In addition, parts of this process will be automated in RIBOLUTION, with the aid of a number of technical innovations (Fig. 1).

Early diagnosis of prostate cancer, to take one example, is usually based on the so-called prostate-specific antigen PSA. If blood PSA levels are elevated, biopsies are taken from the prostate to verify the existence of a carcinoma. The PSA assay, however, is highly unspecific and hence, generates a large number of false-positive results. Furthermore, many prostate carcinomas grow so slowly that an operation could be avoided. Biomarkers that more precisely indicate the existence and aggressiveness of prostate cancer would therefore help avoid unnecessary biopsies and operations.

The University Hospital Dresden has compiled a biobank of tumor samples taken from hundreds of prostate cancer patients. This biobank was used in RIBOLUTION to find novel biomarkers for the disease. It was first exhaustively characterized, which involved the preparation of 200,000 tumor tissue cryosections. These sections were then used to isolate RNA, which was subsequently sequenced using genome-wide next-generation sequencing. Biomarker candidates identified during this procedure were then validated using quantitative real-time PCR. Fig. 2 shows an example of a novel biomarker that exhibits high potential for the (early) diagnosis of prostate cancer. Meanwhile, patent applications have been filed for more than 40 biomarker candidates in RIBOLUTION. In addition to prostate cancer, we are currently also analyzing samples from patients with chronic-obstructive pulmonary disease (COPD) and sepsis.

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1 *A fully automated facility for biomarker validation enables the tiniest volumes of RNA to be accurately analyzed in a high-throughput process.*

2 *A new biomarker for diagnosing prostate cancer compared with the previous PSA marker*

1

Development of a novel, epigenetic cancer therapy based on newly synthesized, non-covalent DNMT inhibitors

The degeneration of healthy somatic cells into malignant cancer cells is closely connected to epigenetic changes in the cells' genome. This includes the hypermethylation of so-called tumor suppressor genes through enzymes which are referred to as DNA methyltransferases (DNMT). Unlike genetic mutations, this type of change, however, can in principle be reversed and therefore presents a promising approach to the development of new drugs.

The project therefore looks at the design, synthesis and the pharmaceutical development of so-called DNA methyl-transferase inhibitors, which intervene in the metabolism of cells and are intended to specifically prevent the hyper-methylation of tumor suppressor genes. Besides a specially developed animal model and modern imaging processes, cancer stem cells (CSC) are also used as part of the development.

Cancer stem cells are regarded as germ cells for the formation and growth of tumors. They are equipped with the characteristics typical of stem cells, such as the ability to self-regenerate or a high differentiation potential. Recent studies allow the assumption that the CSC are particularly resistant to common types of therapy (chemotherapy, radiotherapy) and are therefore responsible for relapses and metastasis. The development of therapy concepts which specifically aim to eliminate CSC is therefore of utmost urgency. The cancer stem cell lines established at the Fraunhofer IZI thus represent an ideal platform for pharmacological development.

As part of the project, the DNMT-relevant target molecules within the CSC-specific signaling pathways are first to be identified and characterized. The DNMT inhibitors identified as being optimal will then be evaluated in a GLP trial on the basis of selected CSC compartments in the animal model. The tumor initiation derived from CSC and the DNMT-based remission of a malignancy can thereby be monitored using bioluminescence imaging. At the same time, the modern imaging procedure allows the entire progress of the disease and therapy within the organism to be observed.

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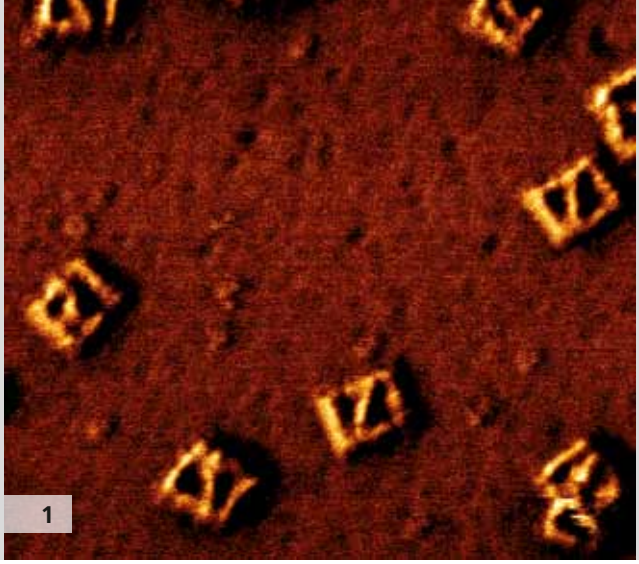
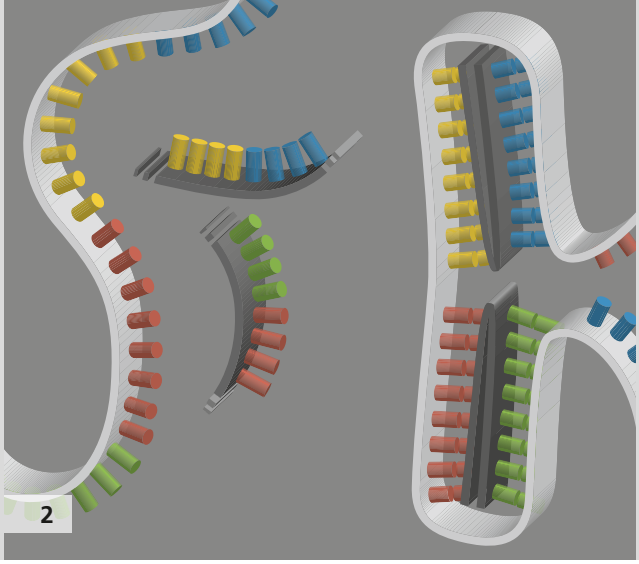
1 *Tumor stem cells*





DNA self-assembly and molecular programming

Currently, the design and construction of tiny objects through the programmed assembly of complementary DNA strands is the most precise and advanced method available for creating arrangements of molecules on the nanometer scale. Through established methods such as the so-called "DNA origami" technique or the assembly of "DNA bricks", lattice-like structural scaffolds can be assembled from DNA strands and used for the placement of nearly any type of molecule on the nanometer scale. This concept of "molecular nanotemplating" using DNA is a powerful technique which has many promising applications in the biomedical fields. The "DNA Nanodevices" unit was established at the Fraunhofer IZI in 2013 within the Fraunhofer ATTRACT program to develop applications for these techniques in the areas of therapeutics and diagnostics.

The "DNA origami" technique utilizes a long, single-stranded DNA scaffold strand of several thousand bases in length, which is folded into a desired shape by hundreds of shorter DNA strands. This is used to create two and three-dimensional structures with an exact shape and size on the nanometer scale. Individual molecules or molecule patterns can be positioned to the nanometer on each of these short DNA strands. This is used to connect tiny carrier molecules, which are able to bind therapeutic anti-cancer drugs, for example, to DNA nanostructures. Other molecules such as aptamers or peptides can be attached to specifically locate diseased cells. The goal is both to increase the efficiency of drugs, as well as to reduce unwanted side-effects on what are normally healthy cells.

Another technique for the assembly of nanoscale structures uses a collection of short, synthetic DNA strands as "bricks". Using this technique, a nearly infinite number of three-dimensional shapes can be constructed from one common collection of DNA strands. The process, from design to final assembly of the nanostructures, has been streamlined and automated with the help of custom software and a liquid-handling robot, so that nearly any shape can be generated within different time frames. An initial application is to use these tiny objects for creating large surfaces of specific topology, upon which arrays of single-walled carbon nanotubes can be precisely arranged. This will enable the creation of DNA-based nano networks, which will form the foundation of miniaturized, ultra-sensitive diagnostic biosensors.

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1 *Atomic Force Microscope (AFM) image of "IZI" Logo drawn onto flat DNA origami by immobilized proteins*
2 *Schematic representation of DNA origami technology*

DEPARTMENT OF DRUG DESIGN AND TARGET VALIDATION

Core competencies of the department

- In silico drug design
- Medicinal and peptide chemistry for the creation of new drugs
- Biomarker identification
- Assay development
- Model development (in vivo and in vitro)
- Pharmacology

A selection of products and services offered by the department can be found on page 68.

IN CONVERSATION WITH PROF. DR. HANS-ULRICH DEMUTH

The Halle department was officially initiated on October 10, 2013. Reaching this stage was no quick process. Which specific challenges had to be mastered in order to found the department? At the end of 2011 the idea came about to transfer the pharmacological/pharmaceutical development expertise, then based at the Bio-Centre in Halle/Saale, to a research society or community. Due to the restructuring of several companies in the local area, there were enough qualified staff available who had often been involved in drug development projects from target validation right through to preclinical and early clinical development. There were also projects awaiting further development and transfer into application. The Fraunhofer Institute for Cell Therapy and Immunology proved itself as a strategic partner and welcomed the project group as new department. Now all that needed to be done was to persuade the State of Saxony-Anhalt and the Fraunhofer-Gesellschaft. This process gradually moved forward between the end of 2011 and the end of 2013 and turned out to be a complicated political, legal, scientific-political and organizational undertaking. A conclusive five-year project and funding plan first had to be prepared, which was reviewed by the governing coalition of the Magdeburg state parliament in terms of strategic and also financial aspects. The successful evaluation led to a letter of intent being send from the Ministry of Sciences and Economic Affairs to the Fraunhofer-Gesellschaft in Munich in autumn 2012. The overall concept and the notified individual projects were then thoroughly checked by internal and external economic and scientific advisers on behalf of the Fraunhofer-Gesellschaft and found to be viable. At the end of May 2013, a binding financial resolution was passed by the State Government of Saxony-Anhalt. The foundation of the new department was then officially announced on October 10, 2013. As part of the opening ceremony, the notification of approval was handed over to the President of the Fraunhofer-Gesellschaft, Professor Reimund Neugebauer, by Minister-President Dr. Reiner Haseloff.

Once founded, the department grew at an incredible speed: after just a few months it was fully operational. How did you manage to recruit enough qualified staff in such a short amount of time? We started looking for qualified staff as soon as we started setting up the department. This involved reading through and evaluating no less than 400 applications which were submitted from all around the world. By the end of 2013 we were able to identify and appoint the core team. This included many members of staff who had previously worked for biotech companies at the same location and had a broad range of experience in the research fields we required as well as good knowledge of the local infrastructure. By the end of the year, the department had grown to comprise a total of 28 members of staff. Due to the huge number of enquiries from master's and PhD students, the team then grew even further to include a maximum of 40 scientific, technical and administrative assistants.

What are the department's core goals for the next five years?

The goals are clear:

1. to consolidate the department and its cooperation with the departments and units in the parent institute. In this respect there are already several areas of common interest, initial approaches and project ideas. Moreover, we want to take the relationships we have with the universities in Halle and Leipzig as well as with Anhalt University of Applied Sciences to a contractual level and further expand the cooperation with the Leibniz institutes IBP in Halle and LIN in Magdeburg in particular. Several members of staff have years of experience working in a teaching capacity at these universities and we are certain that we will be training bachelor's, master's and PhD students in the future.
2. to bring projects which were already planned when the department was set up to a level which will enable us to establish funded projects, industry cooperation projects and academic partnerships at short notice, which will impact on the budget and create the basis for long-term funding beyond the first five years.
3. to make our expertise, scientific nature and results as effective as possible, i. e. by making them visible in high-ranking publications, and thus support the aforementioned activities.

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UNITS

Molecular Biotechnology Unit

The Molecular Biotechnology unit develops and establishes cellular and molecular biology analysis and model systems. This involves cell-based assays, gene expression analysis, immunological and protein chemistry methods, sophisticated cell culture and animal models. The unit conducts a series of cell-based tests for characterizing substances with regard to effectiveness, toxicology and transport. Its service portfolio also includes establishing new animal models for investigating enzyme functions in vivo.

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Protein and Drug Biochemistry Unit

The Protein and Drug Biochemistry unit has in-depth experience in the purification of target proteins as well as their enzymatic characterization. Besides classic protein chromatography procedures, protein chemistry methods are also used, such as the spectroscopic analysis of structure and enzyme-kinetic mode of action. The unit specializes in the humanization of antibodies for the manufacture of protein drugs and their semi-preparative extraction. The subsequent structure-activity-analysis as well as 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 comprises the entire spectrum of medicinal chemistry and analytics required to identify potential, new drug candidates from within the field of "small molecules" and develop them into clinical candidates. Using partly novel computational approaches, potential, new target molecules are first generated in silico and evaluated with regard to their efficacy on the target protein. Once this stage is complete, synthesis and real testing is carried out on the isolated target protein.

The unit offers all prerequisites needed to be able to analytically assist drug development in preclinical and clinical trials. Appropriate parameters can be obtained using liquid chromatography and mass-spectrometry methods. In collaboration with other units, biological assays are being developed and validated, which will allow the success of new types of treatment to be monitored using biomarkers.

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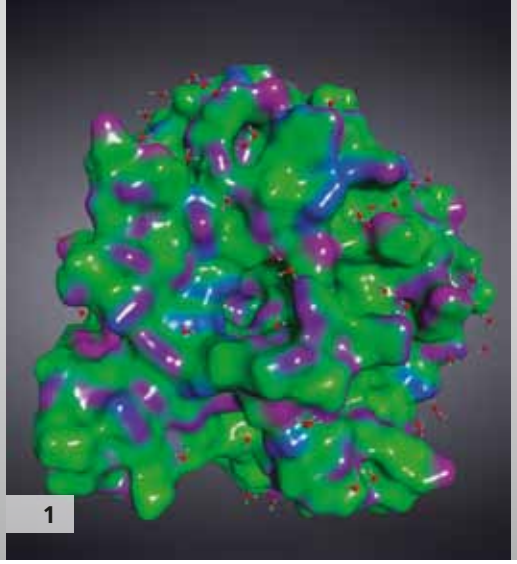

1

PROJECT EXAMPLES

Periodontal pathogens as etiologic factor in RA, CVD and COPD and their impact on treatment strategies

Extensive clinical and epidemiological data clearly show that chronic periodontal disease, one of the most prevalent infectious inflammatory diseases among human beings, is strongly linked to systemic inflammatory diseases such as cardiovascular diseases (CVD), rheumatoid arthritis (RA), and chronic obstructive pulmonary disease (COPD). Taking into account that up to 30% of the adult population worldwide suffers from severe periodontitis, the impact of this disease on human health is immense – an opinion shared by the World Health Organization. Nevertheless, in many European countries periodontitis is a neglected disease, both by the population in general and by health-care personnel. In some cases, this ignorance reaches the stage that hair and tooth loss caused by periodontitis are still considered to be normal, inevitable events associated with aging. To combat this misconception and to research novel ways of treating CVD, RA, and COPD we are exploring the highly innovative idea that these non-infectious diseases are at least aggravated, and maybe even initiated, by periodontal infections.

The project aims to elucidate a relationship between the presence of specific periodontal pathogens and the severity of systemic diseases. Furthermore, it aims to show that extensive periodontal treatment improves the clinical parameters of the investigated systemic diseases. In order to elicit this, specific active agents are to be developed to combat periodontal pathogens, based on bacterial glutaminyl cyclases.

This will reduce mortality while at the same time ameliorating the quality of life of CVD, RA, and COPD patients.

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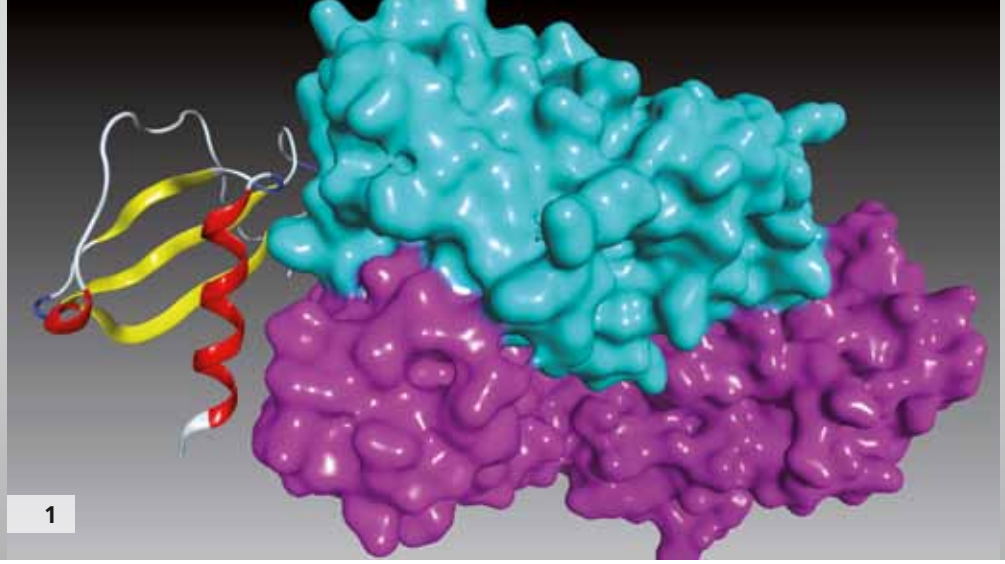
1 *View of the catalytically active center of a bacterial glutaminyl cyclase, a potential target enzyme for the treatment of periodontitis*



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Therapeutic antibodies against active chemokines

Chemokines are signal proteins or peptides secreted by cells, which trigger the migratory movement of immune cells. The secretion of inflammatory chemokines is primarily induced by inflammatory processes and pathogens. This causes the recruitment of leucocytes along a concentration gradient to the source of chemokine production. The dysregulation of chemokines plays a destructive role in many chronic inflammatory diseases such as arthritis, multiple sclerosis and colitis. In this case, however, the high presence of chemokines, which ultimately serve to fight pathogens and damaged tissue, leads to an enhanced influx of immune cells and eventually to these cells attacking endogenous healthy structures.

After cleavage of the signal peptide, some chemokines feature a glutamine as an N-terminal amino acid, which is subsequently transformed into pyroglutamate under physiological conditions through the activity of the glutaminyl cyclases QC and isoQC. The resulting lactam ring is not protonated in the physiological pH range. This provides the respective chemokine with an elevated resistance against aminopeptidases and exoproteases, which need a protonated amino group for substrate binding.

Furthermore, with regard to the above-mentioned chemokines, we were able to demonstrate that the N-terminal pyroglutamate residue facilitates more effective binding to the respective receptors and presumably influences how the proteins fold. Endoproteases, such as matrix metalloproteinases, may, however, still cleave, irrespective of the formation of an N-terminal pyroglutamate. Through this cleavage, physiological antagonists are, however, frequently created which naturally block the receptor and contribute to the remission of the reaction.

Our approach lies in developing protein drugs which neutralize the modified target proteins. Besides the N-terminal modification, other structural elements also come into question here. Additional therapeutic proteins with antibody-like properties will be developed as part of planned collaborations with industry partners.

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1 *Specific binding of an antibody to a chemokine*

DEPARTMENT OF DRUG DESIGN AND TARGET VALDATION

1

Targeting post-translational protein modifications to treat neurodegenerative disorders

Neurodegenerative diseases are characterized by the progressive loss of brain substance. The degeneration of nerve cells is associated with the development of dementia, i. e. a qualitative and quantitative decline of brain cognitive performance. Aging is one of the main risk factors of dementia. Due to constantly increasing life expectancy, demential syndromes, especially Alzheimer's Disease (AD), will pose a major challenge to our health system in the decades to come. Around 1.4 million people are affected in Germany; the global figure is estimated to be around 44 million people and is expected to triple by 2050. Despite the fact that several drugs are now available to extenuate the symptoms of the diseases, there is currently no curative therapy.

Most neurodegenerative diseases are ascribed to a misfolding of proteins, which causes a change in their structure. This structural modification causes a deposit that damages the surrounding tissue and cells, causing them to die off. An effective therapy therefore needs to prevent the peptides from depositing and to accelerate the decomposition of the respective proteins.

The latest research findings show that many of these proteins are prone to changes (post-translational modifications), which often accelerate their deposit. Such modifications include pyroglutamate and isoaspartate formation, nitration or phosphorylation.

This projects aims at identifying post-translational modifications in deposited proteins that are characteristic of the respective neurodegenerative disease. The way in which the modification is formed is to be investigated here and strategies for its suppression are to be deduced. New substances may either prevent the modification of proteins (enzyme effectors) or target the modified proteins by binding to accelerate their degradation (protein drugs).

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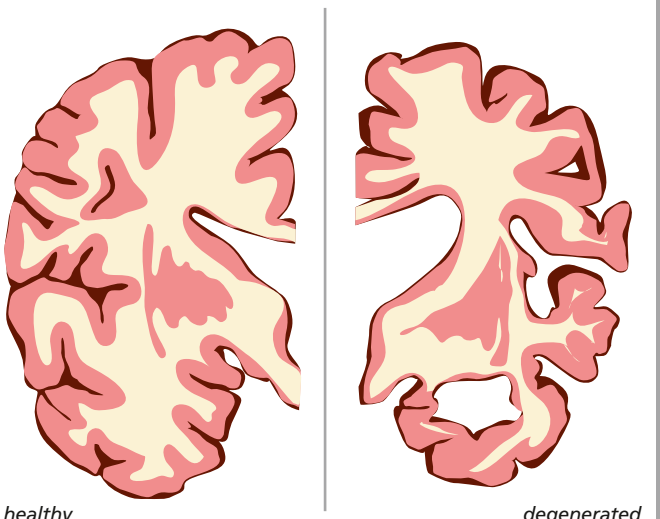
1 *Alzheimer's Disease is associated with a progressive deterioration of cognitive ability. It almost always affects the elderly.*



1

Animal models for inflammatory disorders affecting peripheral organs and the central nervous system

In a number of disorders, pathological alterations are associated with a response from the immune system. Thereby, specialized cells are responsible for recognizing and eliminating damaged or degenerated cells. This process is orchestrated by signal molecules. A number of factors, e. g. genetic predisposition or environmental factors, could lead to these regulated processes becoming part of the pathological changes themselves, either in a causal or supportive role. Besides the deposition of misfolded proteins, such changes, e. g. in Alzheimer's Disease, entail the activation of immuno-competent cells. These cells are able to secrete signal molecules which contribute to the eradication of dead neurons on the one hand, yet which are themselves suspected of damaging healthy neurons on the other.

In addition, a major part of immune response involves the targeted migration of cells to sites of inflammation (chemotaxis). This process is triggered by various signal molecules, which normally demonstrate one or several post-translational modifications. These molecules lead to an increased infiltration of cells to sites of inflammation, for instance in neurodegenerative diseases such as multiple sclerosis or ateriosclerotic changes. Thereby, the analysis of model systems, e.g. of acute peritonitis, can help characterize cell infiltration inhibitors.

In summary, a balance of anabolic and catabolic processes ensures the optimal availability of immune response signal molecules at all times. Pharmacological intervention by altering post-translational modifications may lead to the dampening of inflammatory processes and thus the alleviation of disease symptoms.

As part of the project, various model systems will be established, including humanized mouse models for research into Alzheimer's Disease. The goal is to develop new drugs and treatment concepts.

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1 *Alzheimer's Disease is a degenerative disease affecting the central nervous system which is associated with the loss of cognitive ability. This can be traced back to the deterioration of brain tissue.*

PRODUCTS AND SERVICES

BUSINESS UNITS

The Fraunhofer Institute for Cell Therapy and Immunology IZI explores and develops solutions to specific problems at the interfaces of medicine, life sciences and engineering. To its clients and partners the institute offers complete solutions ranging from market studies right down to the development of a market-ready product and its marketing authorization. In the business units of drugs, cell therapy, diagnostics / assays and biobanks the Fraunhofer IZI develops, optimizes and validates methods, materials and products for medical, biotechnological and pharmaceutical companies as well as for diagnostic laboratories, hospitals and research facilities. On the following pages please find a list of our special competencies, sorted by departments.

Business Unit Drugs

The development of new therapeutic agents is a time- and cost-intensive process. In many cases there is a gap in the transfer of fundamental research results to clinical practice. The Fraunhofer IZI bridges this gap by means of its special know-how in the field of preclinical development. Our range of services already starts with development services and extends over characterization, optimization and preclinical studies right down to clinical trials. Particular priorities are the development of agents in the fields of oncology, infection biology, autoimmune and inflammatory diseases as well as ischemia.

Business Unit Cell Therapy

Cell therapy is the application of cells or cell suspensions. It is the aim of a cell therapy to induce regenerative processes and to replace dysfunctional or defective cells in the patient, respectively. In order to clinically apply cell therapeutics it is required to demonstrate their safety and effectiveness, which is done in extensive preclinical examinations and clinical trials. The Fraunhofer IZI conducts contract development and testing of cell therapeutic methods. The institute offers all developmental steps from one source, from the design of studies over preclinical development right down to the grant of a manufacturing authorization and the production of test preparations for clinical trials.

Business Unit Diagnostics / Assays

In order to promote the development of regenerative therapy strategies innovative diagnostic methods are required. From the characterization of individual cells to the imaging in living organisms, methods and processes must continuously be adapted and adjusted. The Fraunhofer IZI develops, tests and validates new and adapted diagnostic methods and accompanies its partners until a product has reached market maturity. With innovative methods and new classes of biomarkers (e. g. ncRNA) the institute seeks to develop more sensitive, rapid and cost-effective methods and to transfer them to clinical application.

Business Unit Biobanks and Biosystems Technology

Biobanks are collections of biological material that are stored and optionally preserved in a special manner while providing additional information, e. g. about their origin. Biobanks are established for research and other purposes, e. g. as supply for diagnostic or therapeutic methods or, in the field of biology, for the conservation of biodiversity. As far as human materials are concerned, the donators' consent and specific handling regulations are required.

At the Fraunhofer IZI there are biobanks for various inflammatory and tumor tissues as well as for various types of stem cells, also including tumor stem cells, that serve for the processing of research contracts. The units at the Fraunhofer IZI also develop individual components themselves, like for example new cryoprotectors, and are very experienced in conceiving, establishing, documenting and operating biobanks, which are readily utilized within the scope of contracts.

PRODUCTS AND SERVICES

Department of Cell Engineering

- GMP-compliant development and validation of manufacturing processes
- GMP-compliant manufacture of cell and tissue products
- GMP-compliant development and validation of quality controls
- Regulatory consultancy (GMP, GLP)
- Application for tissue procurement permissions according to Section 20b of the German Drug Act
- Application for import permissions from countries outside of the European Union (e. g. for human-derived materials used for manufacturing)
- Assistance in writing the Investigational Medicinal Product Dossier (IMPD)
- Development and validation of pharmacological and immunotoxicological in vitro models (GLP-compliant as required)
- Development and validation of in vivo models for efficacy and safety trials (ATMPs, biological agents, low-molecular active agents; GLP-compliant as required)
- GLP safety trials for immunotoxicity and immunogenicity of pharmaceuticals (ICH S8) and chemicals (REACH) (in vitro/in vivo)
- GLP safety trials for biodistribution and tumorgenicity of autologous and allogeneic ATMPs (in vivo)
- GLP safety trials for immunotoxicity and immunogenicity of allogeneic ATMPs (in vitro/in vivo)
- Validation and beta-evaluation of cell technological procedures/instruments
- Mouse model to record immunotoxicological effects of pharmaceuticals and chemicals (GLP-compliant as required)
- Therapy model (mouse) of salmonellosis (GLP-compliant as required)
- Therapy model (mouse) of sepsis (GLP-compliant as required)
- Therapy models (mouse) of chronic inflammatory bowel diseases (GLP-compliant as required)
- Production of polyclonal rabbit antibodies
- Development of murine and human monoclonal antibodies

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Department of Immunology

- Development of vaccines (antigen, expression systems, adjuvants) for human/veterinary medicine
- Development of diagnostic tests for infectious diseases
- Conditioned humanized/non-humanized mouse
- Model of Graft-versus-Host-Disease (in vivo/in vitro)
- Leukemia model (mouse)
- Skin transplantation model (mouse)
- Human immune system in the animal model (mouse)
- Innovative phage-display libraries
- Enzymatically activatable linker
- Development of diagnostics and therapeutics from peptides
- Epitope mapping of antibodies and mixtures
- Development and manufacture of cell-specific peptides
- Biosensor technology: cell-based early detection of liver failure
- Determination of the hepatotoxicity of drugs

- Determination of albumin function – albumin binding capacity
- Center for clinical trials
- Assay system to isolate biomarkers in the case of arteriosclerosis/development of plaque
- Defensins and antimicrobial peptides
- Modification and biofunctionalization of surfaces (e. g. for cell culture)

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Department of Cell Therapy

- T-cell infiltration patterns in vitro and in vivo
- Cytotoxicity assays
- Cell sorting
- CAM (chorio-allantoic membrane) assay angiogenesis and tumor
- Dye transfer assay
- Large-animal treatment model for cerebral ischemia (sheep)
- Histology of the mammal brain
- Large-animal model for acute cerebral hemorrhage (sheep)
- SNP analysis in the human genome
- Genetic-epidemiological analyses
- Differential allelic RNA expression analysis
- Psychometric testing
- Statistical analyses
- Development of nucleic acid-based assays
- Imaging genetics (combination of (f)MRI and DTI)
- Optimization of the cryopreservation of cells and tissue
- Reprogramming of cells – iPS (induced pluripotent stem cells)
- Screening for anti-aging and tissue-regenerating drugs
- Development of cell therapy – Alzheimer's
- Morphological, functional and spectroscopic examinations in high-field magnetic resonance imaging
- Quantification of in vivo fluorescence and bioluminescence signals
- Stereological cell and object analyses
- Acquisition and evaluation of 3D stacks using confocal laser scanning microscopies
- Development of software-supported evaluation routines (e. g. in MATLAB)
- Animal models of myocardial ischemia
- Model systems of stroke (rat/mouse) – also humanized
- Animal models of vascular dementia
- Multi-dimensional flow-cytometric characterization of organ lysates
- Sensorimotor and cognitive behavioral tests

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Department of Diagnostics

- Model for acute and chronic arthritis (mouse, rat)
- Cartilage destruction models (mouse)
- Cellular functional testing for tissue-destructive fibroblasts
- Allergic rhinitis model (mouse)
- Scleroderma model (mouse)
- Humanized NSG mouse
- Model of chronic and acute allergic asthma (mouse)
- Model of chronic obstructive lung disease (COPD)
- Model of sepsis in the humanized NSG mouse
- Model of xenogeneic Graft-versus-Host-Disease in the NSG mouse
- Cytostatics/in vitro testing on tumor stem cells
- Personalized tumor killer cells
- Cytostatics and cell therapeutics
- Nanostructuring of surfaces
- Optimization of pathogen isolation methods
- Development of molecular diagnostic detection procedures
- Functional nanoparticles in diagnostics and therapy
- Development of diagnostic rapid tests
- Sepsis diagnostics
- Transcriptomic analyses using tiling arrays and ultra high throughput sequencing
- Microarray analytics
- MicroRNA analytics (expression, localization, targets)
- Non-coding RNA – biomarkers
- Non-coding RNA – therapy targets
- Design and synthesis of nano-objects on DNA basis ("DNA origami")
- Mesoporous silicon for drug delivery

Contact: Prof. Dr. Friedemann Horn | Phone +49 341 35536-3305
friedemann.horn@izi.fraunhofer.de

Department of Drug Design and Target Validation

- Development and phenotyping of transgenic animal models
- Animal pharmacology
- Mammalian cell culture
- Primary cell culture
- FACS analyses
- RT-PCR
- Immunocytochemistry
- Immunohistochemistry
- Microscopy (bright field and confocal)
- Manufacture (cloning) of expression vectors
- Heterologous expression of proteins in E. coli, yeast, insect cells and mammalian cells
- Protein purification using column chromatography
- Spectroscopic analysis of enzyme structure and function in vitro (UV-Vis, CD, and fluorescence spectroscopy)
- Development of enzyme assays
- Structure-based optimization of antibodies (protein engineering)
- Rational drug design in silico
- Synthesis, purification and analysis of small molecules
- Synthesis, purification and analysis of peptides/proteins (MALDI-TOF/TOF)
- High performance liquid chromatography – mass spectrometry analysis (LC-ESI-MS)
- Physico-chemical analysis of protein-ligand interactions
- Identification of biomarkers
- Assay development and method qualification for preclinical and clinical studies

Contact: Prof. Dr. Hans-Ulrich Demuth | Phone +49 345 131428-00
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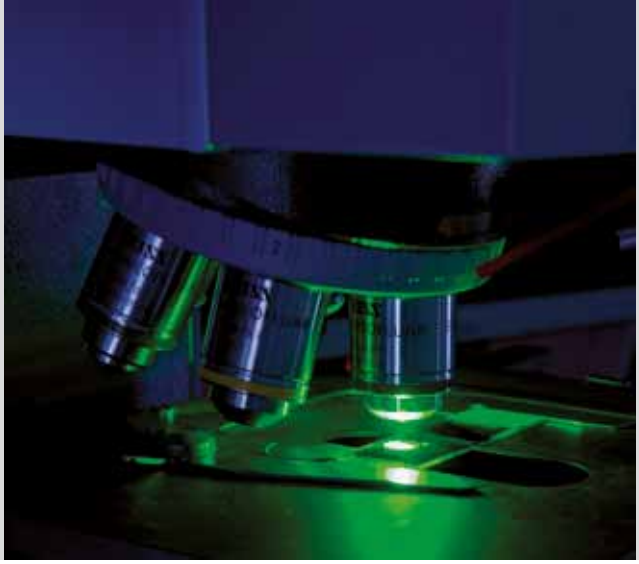
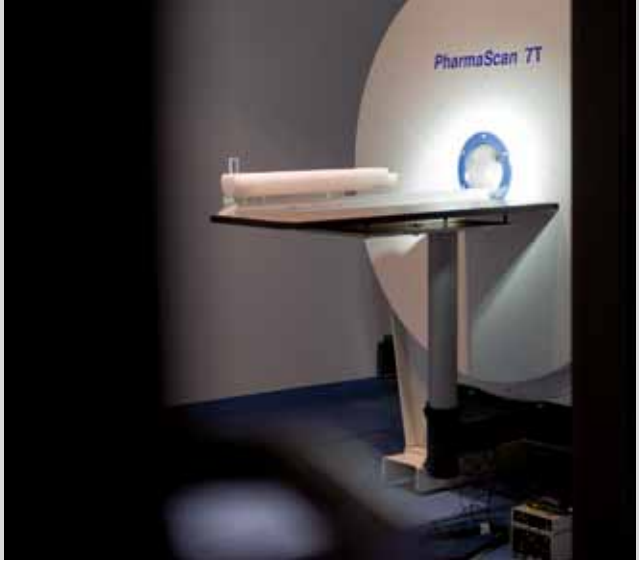




Excerpt of the equipment pool at the Fraunhofer IZI

Cell biological
- Bioreactors (partially automated)
- Cell separation/cell sorting
- Real-time Cell Analyzer (xCELLigence)
- GLP-compliant cell and biomaterial bank
- Cell culture

Molecular biological
- Fermenter for DNA and protein production
- Affinity measurements (BIACORE)
- Protein purification and separation (ÄKTA avant)
- High-throughput sequencing (Illumina's MiSeq)
- Pool of PCR and electrophoresis instruments (incl. real-time PCR)
- Expression analysis systems
- Microarray scanners and hybridization stations
- Proteome analytics
- Reporter gene studies

Imaging
- Immunohistochemistry/histology
- Fluorescence/confocal microscopy
- C-arm X-ray unit
- 7-tesla high-field magnetic resonance imaging system (small animal)
- Atomic force microscopy
- Bioluminescence imaging (Caliper/Xenogen Spectrum 200)

GMP
- Class A, B, C and D modular, pharmaceutical clean rooms
- DQ/IQ/OQ-qualified equipment for quality control
- DQ/Q/OQ-qualified equipment for the production of cell therapeutics

Medicinal chemistry
- Mass spectrometry (ESI-MS/MS and MALDI-TOF/TOF)
- Peptide synthesizer
- Isothermal titration calorimeter
- High performance liquid chromatography (HPLC)
- IT infrastructure for in silico drug design

Others
- In vivo electroporation
- Large animal OP
- Small animal OP
- Bioinformatics and biostatistics
- BioTechFlow System (simulation of vascular flow)
- Cryopreservation

FACILITIES AND BUILDINGS

With a communicative infrastructure, state-of-the-art laboratory clusters and an extensive equipment pool on hand, the Fraunhofer IZI can offer a broad range of research activities and services.

The institute building

The Fraunhofer IZI consists of two buildings which are connected to each other and also to the neighboring BIO CITY via a total of three bridges. The modern main institute building was completed and put into operation in 2008. The first extension building was completed and moved into in November 2012. As well as excellent working conditions, the buildings offer institute personnel a communicative infrastructure, prompting interdisciplinary exchange between units. A spacious seminar area and a representative atrium in the main building also allow various advanced training formats and scientific events to be carried out, such as the Fraunhofer Life Science Symposium. The first extension building is equipped with laboratories for experimental medicine which cover an area of 1,200 m².

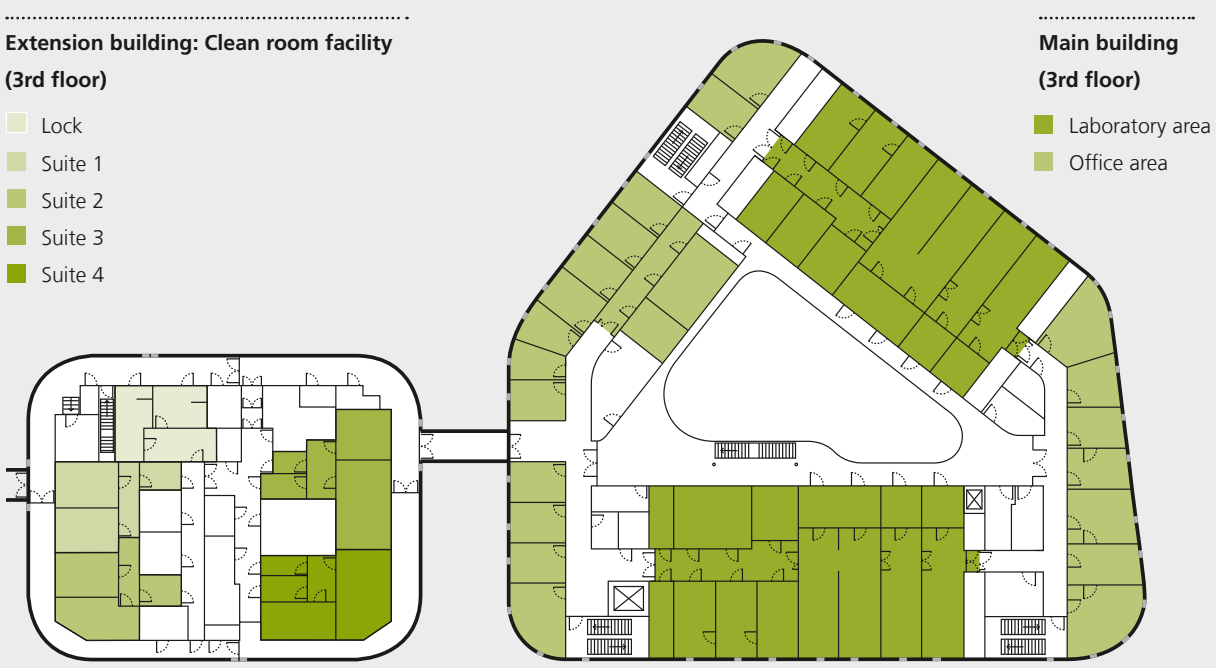
Construction work for a third building phase has now been ongoing since the start of 2013. This phase will add another 1,600 m² of laboratory space. Besides an additional clean room facility, plans are also in place for an S3 infection biology laboratory and a technical center for optimizing processes in cell-oriented medical technology.

Laboratory capacities

The Fraunhofer Institute for Cell Therapy and Immunology boasts state-of-the-art laboratories. They are particularly well equipped for working in the areas of molecular biology, biochemistry, cell biology and immunology. An extensive immunohistochemistry laboratory, an isotope laboratory, a quality control laboratory with qualified equipment, as well as cyrostorage capacities round off the main building's facilities. The first extension building includes a considerable experimental medicine area which is suitable for establishing and testing small and large animal models. A GMP facility and an expansive equipment pool for all kinds of imaging procedures (e. g. magnetic resonance imaging) complete the research unit.

All of the Fraunhofer IZI's laboratories are certified according to S2 standards and therefore suited to work in the fields of genetic engineering and infection biology. A flexible cluster structure allows laboratory sections to be adapted to and fitted in line with the specific requirements of a broad range of projects. The institute occupies a 3,500 m² laboratory area.

Floor plan of the Fraunhofer IZI, main building and first extension building:



Clean room facilities (GMP)

The Fraunhofer IZI operates two clean room facilities with an overall surface area of 750 m². Both facilities are designed for the GMP-compliant manufacture of cell-based medicinal products for clinical trials. The facility is separated into different suites where work can be conducted in line with cleanliness class A. The facility's modular structure allows different projects to be handled in parallel and independently of one another.

Branch labs

The Fraunhofer IZI operates branch labs based in Halle/Saale (Saxony-Anhalt) and Rostock (Mecklenburg-Western Pomerania), which have access to over 1,300 m² of laboratory and office space in Halle and 600 m² in Rostock in laboratories rented from regional biocenters.

1 *Main building of the Fraunhofer IZI in Leipzig*
2 *Branch lab in Halle/Saale*
3 *Branch lab in Rostock*

TECHNOLOGY PLATFORMS

With extensive competencies and a state-of-the-art equipment pool, the institute is able to offer research services along the entire value chain of a specific technology.

Antibody development

Antibodies identify antigens through a highly specific binding. This makes them interesting tools in biology, medical research and in both treatment and diagnostics.

The Fraunhofer IZI develops and produces antibodies for therapeutic and diagnostic use. Therapeutic antibodies have been mainly used for treatment of different kinds of tumors and lymphomas, treatment of rheumatoid arthritis, Crohn's disease, and asthma, and in the prevention of rejection after organ transplantation.

Antibodies are an essential research tool used in test kits for the detection of soluble or cell-linked marker molecules. They can be modified to change their compatibility or biological characteristics. For in vivo diagnostics as well as functional extension of therapeutic antibodies different methods can be used to link signal and effector molecules.

In order to facilitate tolerance, the Fraunhofer IZI is also developing human monoclonal antibodies with the desired specificities.

Research
- Qualified research and market analysis of a specific field of application
- Identification of competitor products, estimation of the size of a market, detection of market niches and the offering of targeted solutions

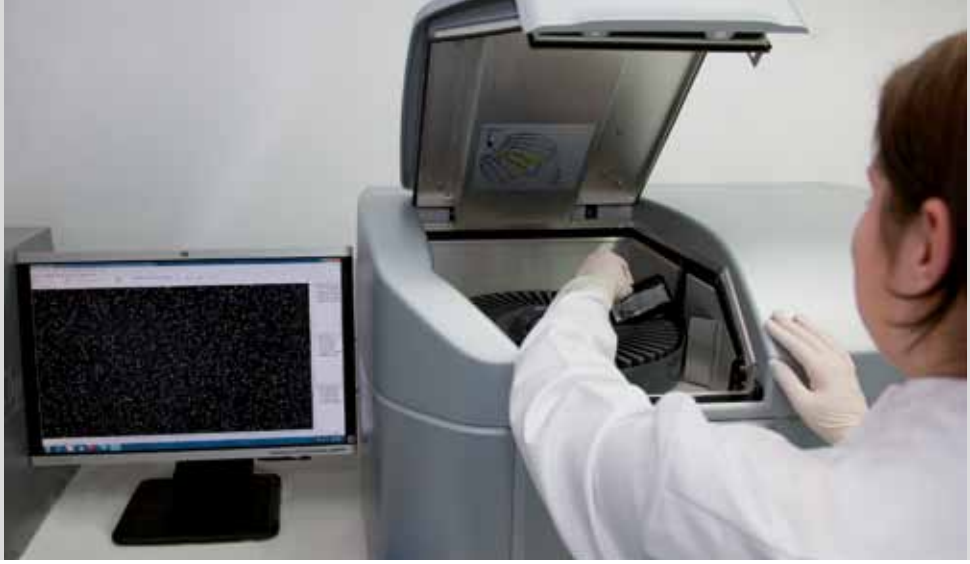
Target indentification
- Identification of target molecules
- Qualification of corresponding epitopes
- Testing of effectiveness in laboratory scale

Production
- Generation and production of polyclonal and monoclonal antibodies
- Optimization through molecular biological methods and/or labelling

Documentation
- GLP-compliant documentation
- Development of protocols and SOPs

Process development
- Development of a GMP-compliant production process
- Production of investigational medicinal products in compliance with § 13 of the German Pharmaceutical Act (AMG)
- Establishment of master- and working cell banks

Clinical trial
- Design and performance of clinical trials (phase II und III) are supported by the institute



Biomarker tests

Biotechnological and biomedical research as well as pre-clinical and clinical trials require validated high throughput analysis methods for detection of biomarkers, drugs and genes. It is important to analyze samples of different origins as rapidly as possible with a high precision. Because customer demands vary widely, the development of a universal test is far away. The Fraunhofer IZI bundles competencies to offer a broad spectrum of analysis methods to its partners.

Therefore existing technology platforms can be combined individually for the seperate requirements of each customer. New analysis methods are then developed in cooperation with the partner. The modern, high-end equipment and the broad competencies of the institute make it a strong partner in assay adaptation and development and screening, of pharmaceutical agents as well as in diagnostics and monitoring. Therefore the complete developmental process, from identification of target molecules to clinical validation of the assay, is represented by the institute.

A unique selling point is the special expertise of the Fraunhofer IZI in RNA technologies. Non-coding RNA (ncRNA) has recently become more important as it can be used as significant biomarkers for either tumor detection or as a new therapeutic target.

Identification of target molecules

- Identification of eligible target proteins or genes associated specifically with a disease

Biomarker development

- Design and synthesis of sensors with high affinity and specificity for a target

Adaption of analytical platforms

- Adaptation of existing (proteomic or genomic) technology platforms for specific assay conditions

Optimizing parameters

- Optimization of the assay in regards to specific sensitivity, speed and costs

Evaluation

- Evaluation of the assay through patient samples in the laboratory according to the gold-standard

Clinical validation

- Validation of the assay with patient samples in clinical environment

Vaccine development

Vaccines and diagnostic assays are elemental methods for combating infectious diseases, in both human and veterinary medicine.

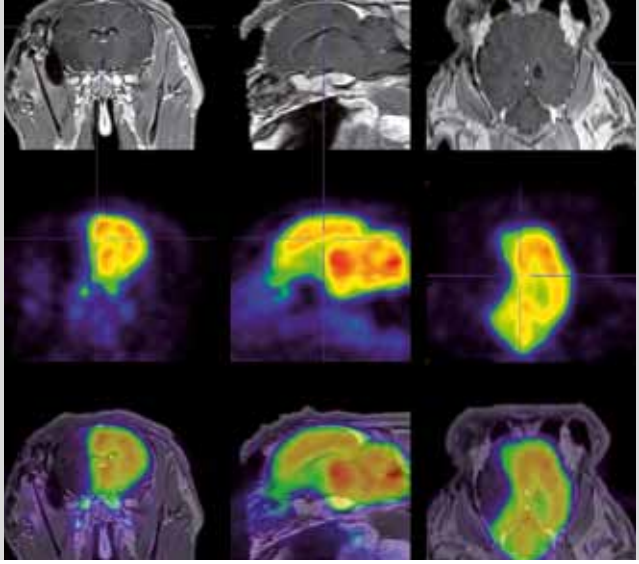
The Fraunhofer IZI's activities in the development of vaccines range from the selection and optimization of suitable antigens right down to the conduct of proof-of-principle tests in various animal models. Pathogens from the fields of virology, bacteriology and parasitology can be processed. Models of ectoparasites (e. g. mites) are also established at the institute.

The Fraunhofer IZI's know-how comprises state-of-the-art vaccine technologies like DNA, recombinant subunit or vector vaccines. In veterinary medicine it is often decisive to distinguish between vaccinated animals and naturally infected animals (DIVA principle, differentiation of infected and vaccinated animal). This is ensured by the methods available at the Fraunhofer IZI.

For the testing of vaccine candidates we have at our disposal small and (due to a close cooperation with the Faculty of Veterinary Medicine at the Leipzig University) large animal models.

For the serological detection of pathogens the Fraunhofer IZI recombinantly produces antigens which are then optimized for diagnosing by in vitro tests. On the one hand this allows for examining the effectiveness of our vaccine candidates. On the other hand this technology platform offers the possibility to develop novel serological assays (e. g. ELISAs).

- Cultivation of pathogens
- Display of antigens
- Design of vaccine vectors/proteins
- Small animal models for immunizations
- Large animal models for veterinary vaccines
- Characterization of the immune response
- Fine mapping and optimization of epitopes
- Design of accompanying serological assays



Ischemia models

Meaningful model systems are required for the development of therapeutic strategies and diagnostic methods in the field of cerebral and cardiac ischemia. Especially for the prevention of failures and costs in the technology transfer area it is crucial to minimize risks and sources of error already in the course of preclinical development.

The Fraunhofer IZI offers different model systems for addressing a variety of aspects within the development chain. Apart from various in vitro models this also applies to a number of in vivo models. As the transfer of research results from a small animal model to human applications led to a number of failures in the past, a large animal model that is much closer to the human physiology has been developed at the Fraunhofer IZI.

Comprehensive equipment and cooperations in the area of medical imaging have rendered the institute capable of evaluating both regenerative processes and diagnostic applications in vivo.

The institute is particularly specialized in, but not limited to, the development of cell therapeutic methods. Our service portfolio also comprises the testing of agents, surgical therapy methods and the development of new imaging methods.

- Modular design of preclinical studies
- Complete implementation of STAIR criteria
- Adaptation and evaluation of models
- Conduct of studies according to clinical standards
- Monitoring of studies and data management
- Concept assessment and evaluation

Model systems

In vitro models
- e. g. for the identification of neuroprotective effects

In vivo model (rodentia)
- e. g. cell transplantations, behavior analyses, magnetic resonance imaging, histology

In vivo model (ovine)
- e. g. long term studies, utilization of adult autologous stem cell populations, magnetic resonance imaging

QUALITY MANAGEMENT

With a highly successful quality management the Fraunhofer IZI fulfills its clients' and partners' sophisticated demands and thus guarantees research services at the highest level.

GLP – "Good Laboratory Practice"

"Good Laboratory Practice" (GLP) is a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. This is the definition of Good Laboratory Practice in the GLP principles of the Organization for Economic Co-operation and Development (OECD) that were devised following the EC-Directive, which was incorporated into German legislation for chemical compounds ("Chemikaliengesetz"). Good Laboratory Practice, as almost no other quality system, has contributed to health, environmental and animal protection through its worldwide implementation and the consequent widely reciprocal recognition of study data.

Fraunhofer IZI holds a separate GLP laboratory and trained personnel. These resources are fully equipped to provide integrated solutions for research and development.

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GMP – "Good Manufacturing Practice"

The Fraunhofer IZI maintains two GMP-compliant clean room facilities. Through the flexible design, the facility is especially attractive for new biotechnology companies that seek to bring newly developed medicinal products into clinical application via clinical trials. The facility is 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 transport) 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-based therapeutics (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 according to § 13 of the German Drug Act (AMG).

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Why are GMP and GLP important?

The clinical trial of new drug candidates is an essential step on the way to approval. Since the 12th revision of the "Arzneimittelgesetz AMG" (German Drug Act) every clinical drug 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-Institute) and by the responsible ethics commission 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 pre-clinical 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.

GCP – "Good Clinical Practice"

GCP describes internationally accepted regulations which govern the execution of clinical trials. These regulations encompass ethical as well as scientific aspects. Clinical trials are divided into three phases.

- Phase I: Establishment of safety of the new medication/therapeutic
- Phase II: Establishment of the efficacy of the new medication/therapy (Phase IIa) and dose curve (Phase IIb)
- Phase III: Establishment of a significant proof of efficacy (also known as Pivotal-trial).

Only after successful completion of phase III can new substances register for marketing approval. All phases of clinical development must be carried out under the above described GCP-guidelines. The protection of the patient or volunteer must always remain in the foreground. Important aspects of this include the patient consent form, patient trial insurance as well as the exact documentation of the trial results. Additionally GCP regulates the roles of the essential entities involved in the trial including the sponsor, monitor, CRO, primary investigator and ethics committee or intuitional review board and also regulates quality management and adverse event reporting.

The Fraunhofer IZI carries out in cooperation with doctors and SMO's (site management organizations) clinical trials as requested by Sponsors. The Fraunhofer IZI is a reliable partner in the area of clinical trial planning, composition of trial protocols and all other necessary documents required for submission to the regulatory authorities including the ethics committee. Private physicians and SMOs carry out on-site patient visits.

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frank.emmrich@izi.fraunhofer.de

SPIN-OFFS AND COMPANY SETTLEMENTS

The Fraunhofer IZI strengthens the regional economy by helping international and national companies settle in Leipzig and by supporting and encouraging colleagues in starting up their own companies.

Since its foundation in 2005, the Fraunhofer IZI has been substantially involved in the settlement and founding of a total of eleven companies. The site's appeal and its local cooperation with the Fraunhofer IZI were important factors in the partners' decision to settle there.

ApoCell (settled in 2013)

- Origin: USA, ApoCell Inc.
- Business model: development of a procedure to improve cancer diagnostics

Bioville GmbH (founded in 2010)

- Origin: Germany, Fraunhofer IZI
- Business model: developing and managing projects with a focus on the former trade fair grounds

Cognate Bioservices GmbH (settled in 2011)

- Origin: USA, Cognate BioServices, Inc.
- Business model: providing development services for cell therapy products

InnovaStem GmbH (settled in 2009)

- Origin: Italy, I.M.S. Innovative Medical Solutions S.r.l.
- Business model: establishing a stem cell bank to store adult stem cells from various neonatal tissues

Magna Diagnostics GmbH (founded in 2010)

- Origin: Germany, Fraunhofer IZI
- Business model: developing an innovative diagnostics platform for the rapid diagnosis of infectious diseases based on a lab-on-a-chip system

MD-5 GmbH / Nervive (settled in 2012)

- Origin: USA
- Business model: medical device for stroke therapy

Northwest Biotherapeutics GmbH (settled in 2011)

- Origin: USA, Northwest Biotherapeutics, Inc.
- Business model: developing an immunotherapeutic to treat glioblastomas

Nuvo Research GmbH (settled in 2009)

- Origin: Canada, Nuvo Research Inc.
- Business model: developing immunomodulatory drugs to treat inflammatory diseases such as rheumatoid arthritis and allergic rhinitis

Oncotrition GmbH (founded in 2012)

- Origin: Germany, Fraunhofer IZI
- Business model: nutritional supplement concepts for the prevention of cachexia and the development of tumor-preventative strategies

Prima BioMed GmbH (settled in 2010)

- Origin: Australia, Prima BioMed Ltd.
- Business model: developing an immunotherapeutic to treat ovarian cancer

SelfD Technologie GmbH (settled in 2012)

- Origin: Estonia, Selfdiagnostics, OÜ
- Business model: in vitro diagnostics

Sonovum AG (founded in 2011)

- Origin: Germany, Fraunhofer IZI
- Business model: developing diagnostic procedures
- on the basis of ultrasounds

PARTNERS

ACOMED Statistik, Leipzig ■ AJ Roboscreen GmbH, Leipzig ■ ALS Automated Lab Solutions GmbH, Jena ■ Analytik Jena AG, Jena ■ AnaPath GmbH, Oberbuchsiten, Switzerland ■ ApoCell, Houston, USA ■ Apraxon GmbH, Hofbieber ■ AptaIT GmbH, Munich ■ ASA Spezialenzyme GmbH, Wolfenbüttel ■ Baxter Oncology GmbH, Halle/Westfalen ■ Becit GmbH, Bitterfeld-Wolfen ■ Bombastus-Werke AG, Freital ■ BSL Bioservice GmbH, Planegg/Munich ■ Charité, Berlin ■ Cognate Bio Services, Inc., Memphis, USA ■ Compart Umwelttechnik GmbH, Weißenfels ■ Cytori Therapeutics Inc., San Diego, USA ■ DMCE GmbH & Co KG, Linz, Austria ■ EPO Berlin Buch GmbH, Berlin ■ ERT-OPTIK Dr. Thiel GmbH, Ludwigshafen ■ euroderm GmbH, Leipzig ■ Evercyte GmbH, Vienna, Austria ■ FrimTec GmbH, Oberostendorf ■ Genetic Immunity Kft., Budapest, Hungary ■ GESA Automation GmbH, Teuchern ■ ibidi GmbH, Martinsried ■ Idifarma Desarrollo Farmacéutico, S.L., Navarra, Spain ■ IDT Biologika GmbH, Dessau-Roßlau ■ IkerChem S.L., San Sebastian, Spain ■ InnovaStem GmbH, Leipzig ■ Lake Bioscience, Grayslake, USA ■ Lipocalyx GmbH, Halle/Saale ■ Magna Diagnostics GmbH, Leipzig ■ MD-5 GmbH, Leipzig ■ microfluidic ChipShop GmbH, Jena ■ Micron Research Service, Venturina, Italy ■ Northwest Biotherapeutics, Inc., Bethesda, USA ■ Novavax AB, Uppsala, Sweden ■ Nuvo Research GmbH, Leipzig ■ Oncotrition GmbH, Leipzig ■ Phoenix Biomedical Products Inc., Mississauga, Canada ■ pluriSelect GmbH, Leipzig ■ PolyBatics, Ltd., Palmerston, New Zealand ■ Polyquant GmbH, Bad Abbach ■ Praxis Biopharma, Miñano, PT Alava, Spain ■ Praxis Prof. Dr. Hoheisel, Leipzig ■ Prima BioMed GmbH, Leipzig ■ Prima BioMed Ltd, Sydney, Australia ■ Probiodrug AG, Halle/Saale ■ RESprotect GmbH, Dresden ■ Siemens AG, Munich/Erlangen ■ Sonovum AG, Leipzig ■ SynAffix B.V., Nijmegen, The Netherlands ■ Tavarlin AG, Pfungstadt ■ Vita 34 AG, Leipzig ■ Vivotecnia Research S.L., Tres Cantos/Madrid, Spain ■ XanTec bioanalytics GmbH, Düsseldorf

SCIENCE LOCATION LEIPZIG

LEIPZIG AND THE FORMER TRADE FAIR GROUNDS

The Fraunhofer Institute for Cell Therapy and Immunology IZI is located on the former trade fair grounds in the south-east of the city of Leipzig. Close cooperation with the nearby facilities of the Leipzig University and the companies of the BIO CITY Leipzig is maintained.

Location: Central for interface partners

The Fraunhofer Institute for Cell Therapy and Immunology IZI is located on the former trade fair grounds in the south-east of the city of Leipzig. The institute's premises are only about a ten-minute drive away from the city center and can easily be reached with public transport. Moreover, many of the already established and potential future cooperation partners are located in the immediate vicinity. Among these are, for example, the BIO CITY Leipzig, the Max Planck Institute for Evolutionary Anthropology, the clinics and institutes of the Medical Faculty, the Chemistry Faculty, the Physics Faculty, the Veterinary Medicine Faculty, as well as the Faculty of Life Sciences, Pharmacy and Psychology.

BIO CITY Leipzig: A potent neighbor

The BIO CITY Leipzig unites university and industry-related research under one roof. It houses, for instance, the Biotechnological-Biomedical Center (BBZ) of the Leipzig University and has available space for industrial settlements in the vicinity. More than 25 cell technology companies including VITA34 International AG, Haemabank AG and Curacyte AG are already located there. Cooperations with the Fraunhofer IZI have been established in the fields of cell engineering and applied stem cell biology, bioprocess engineering, protein structure analysis, mass spectroscopy, molecular cell therapy and molecular pathogenesis.

Integrated universities

The academic landscape within Leipzig also benefits from cooperation with the Fraunhofer IZI: The Leipzig University, the Leipzig University of Applied Science (HWTK) and the Graduate School of Management (HHL) have found in the Fraunhofer IZI a strong partner for research cooperations and the development of joint programs for teaching and advanced vocational training, which enhance local attractiveness from an economic and scientific point of view. Thus, for example, students of business administration from the HHL have already been successfully involved in practical scientific projects with their development of business plans or marketing concepts. A particularly intensive cooperation connects the Fraunhofer IZI and the Institute for Clinical Immunology and Transfusion Medicine (IKIT) of the University Leipzig.

The outstanding collaboration work with the Faculty of Veterinary Medicine and its institutes and clinics directly opposite the Fraunhofer IZI building deserves special mention. Research involving animal experiments does not only serve the development of new products for human medicine, but also contributes to the development of new diagnostic and therapeutic procedures in veterinary medicine.

The Faculty of Medicine has traditionally been an extremely important partner with many interactions, also in teaching and advanced education. The Fraunhofer IZI has been working closely together with institutional and clinical areas of radiology, nuclear medicine and diagnostics for several years now in order to develop sophisticated imaging procedures for large animal models.

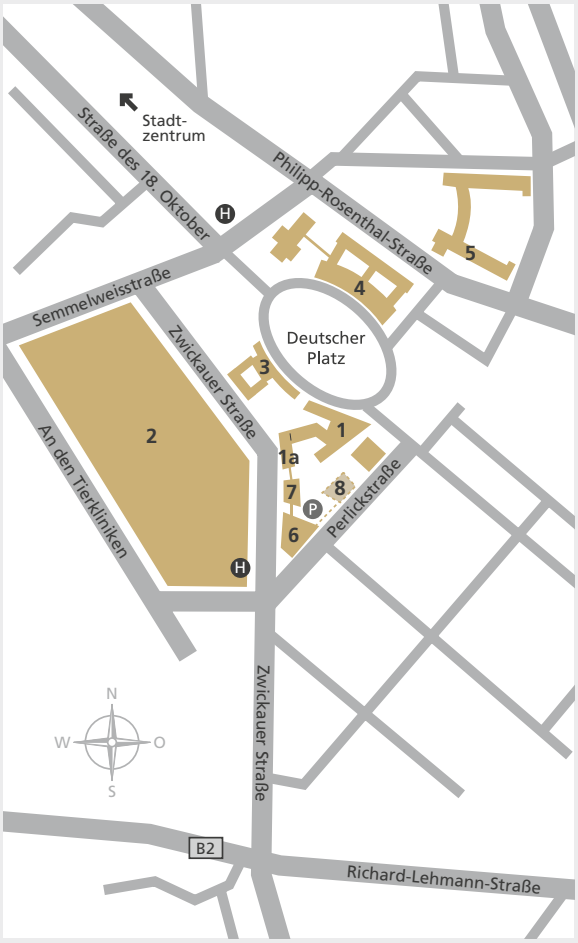
Excellence partner: Translational Center for Regenerative Medicine

One of the most important partners of the Fraunhofer Institute for Cell Therapy and Immunology IZI is the Translational Center for Regenerative Medicine (TRM), which was founded within the framework of the Excellence Initiative 2006 by the German Federal Ministry of Education and Research and the Free State of Saxony. Under the auspices of the renowned immunologist Prof. Dr. Frank Emmrich, institutes from five faculties established the TRM in order to start conceptional, pre-clinical and clinical research projects focused on Tissue Engineering and Materials Sciences (TEMAT), Cell Therapies for Repair and Replacement (CELLT), Regulatory Molecules and Delivery Systems (REMOD), Imaging, Modeling, and Monitoring of Regeneration (IMONIT). In 2010, the TRM received a very

positive evaluation by the consulting firm Capgemini Deutschland Holding GmbH and international consultants, so that funding was granted by the BMBF and Saxony for further support.

Numerous partners in the immediate vicinity

The neighboring partners of the Leipzig University are, among others, the Translational Center for Regenerative Medicine (TRM) and the University Hospital (special field of transplantation). Further institutions relevant for cooperation are the Heart Center Leipzig GmbH, the Helmholtz Center for Environmental Research (UFZ), the Leibniz Institute for Surface Modification (IOM), the Interdisciplinary Center for Bioinformatics (IZBI), the Center for Clinical Trials Leipzig GmbH (ZKS), the Center for Therapeutic Studies (ZET) and the Leipzig Interdisciplinary Research Cluster of Genetic Factors, Clinical Phenotypes and Environment. Moreover, there are numerous interfaces with different special research areas and so-called Transregios (transregional research projects) that are located in Leipzig.



BIO CITY (1) with hired Fraunhofer IZI area (1a), Faculty of Veterinary Medicine, institutes and hospitals (2), Max Planck Institute for Evolutionary Anthropology (3), German National Library (4), Translational Centre for Regenerative Medicine (5), Fraunhofer IZI (6), 1. extension Fraunhofer IZI (7), 2. extension Fraunhofer IZI (8).

Translational Centre for Regenerative Medicine (TRM)
Philipp-Rosenthal-Str. 55 | 04103 Leipzig
www.trm.uni-leipzig.de

Interdisciplinary Centre for Clinical Research (IZKF)
Liebigstr. 21 | 04103 Leipzig | www.izkf-leipzig.de

Center for Biotechnology and Biomedicine (BBZ)
Leipzig University | Center for Biotechnology and Biomedicine | Deutscher Platz 5 | 04103 Leipzig
www.bbz.uni-leipzig.de

University Hospital Leipzig AöR
Liebigstr. 18 | 04103 Leipzig | www.uniklinik-leipzig.de

Heart Center Leipzig GmbH – University Hospital
Strümpellstr. 39 | 04289 Leipzig
www.herzzentrum-leipzig.de

Coordination Center for Clinical Trials Leipzig (ZKS)
Leipzig University | Härtelstr. 16–18 | 04107 Leipzig
www.kks.uni-leipzig.de

Interdisciplinary Center for Bioinformatics (IZBI)
Leipzig University | Härtelstr. 16–18 | 04107 Leipzig
www.izbi.uni-leipzig.de

Max Planck Institutes (MPI)
Max Planck Institute for Human Congnitive and Brain Sciences | Post office box 500355 | 04303 Leipzig
www.cbs.mpg.de

Max Planck Institute for Mathematics in the Sciences
Inselstr. 22 | 04103 Leipzig | www.mis.mpg.de

Max Planck Institute for Evolutionary Anthropology
Deutscher Platz 6 | 04103 Leipzig | www.eva.mpg.de

Helmholtz Center for Environmental Research GmbH – UFZ
Permoserstr. 15 | 04318 Leipzig | www.ufz.de

Leibniz Institute for Surface Modification e.V.
Permoserstr. 15 | 04303 Leipzig | www.iom-leipzig.de

Association for the Advancement of the Health Economics of the Region Leipzig (VGF) e.V.
Deutscher Platz 5a | 04103 Leipzig | www.med-in-leipzig.de

Leipzig University
Ritterstr. 26 | 04109 Leipzig | www.uni-leipzig.de

Faculty of Medicine
Liebigstr. 27 | 04103 Leipzig | www.medizin.uni-leipzig.de

Faculty of Biosciences, Pharmacy and Psychology
Brüderstr. 32 | 04103 Leipzig | www.uni-leipzig.de/~biowiss

Leipzig University of Applied Sciences (HTWK)
Karl-Liebknecht-Str. 132 | 04277 Leipzig
www.htwk-leipzig.de

Graduate School of Management (HHL)
Jahnallee 59 | 04109 Leipzig | www.hhl.de

EVENTS

THE FRAUNHOFER IZI IN PUBLIC

Events are the key ingredient of the institute's communication strategy. The Fraunhofer IZI once again organized and supported various scientific and public events in 2013.

January 23, 2013: New Year reception / opening of the second extension building

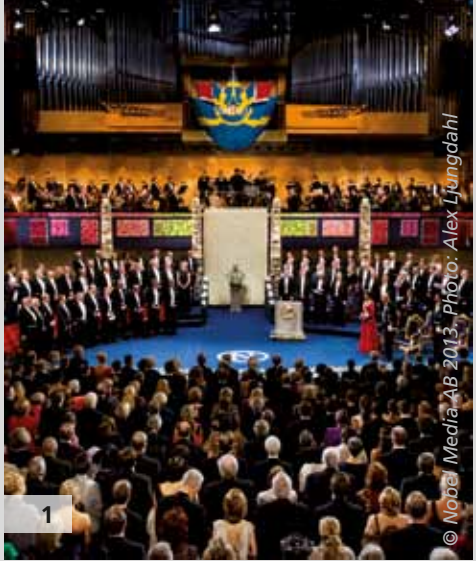
The ceremonial opening of the institute's second extension building held at the very beginning of the year was a welcome occasion to get a new tradition up and running. Together with its sister institute in Leipzig, the Fraunhofer Center for Central and Eastern Europe (MOEZ), the Fraunhofer IZI invited guests to the Leipzig Fraunhofer institutes' first ever joint New Year reception. Both institutes have been firmly anchored in the local research landscape for many years now and contribute to the region's potential for innovation. Through regional and international cooperation work and contract research projects, the institutes boost the visibility of Leipzig. This can only work based on a solid regional network and strong partners in business, politics, research and medicine.

In order to nurture and maintain this network, but also to say thank you to our partners and customers for their trusting collaboration, both of the Leipzig Fraunhofer institutes initiated the New Year reception. Guests from both institute networks came together in a relaxed and informal setting. The event presented an excellent opportunity to highlight achievements and discuss plans and future visions. The event location will alternate between the Fraunhofer institutes. The second event will thus take place on January 15, 2014 at the Fraunhofer MOEZ.

March 20, 2013: workshop held by Saxon Minister of State for Science and the Arts, Professor Sabine Schorlemer, together with Sonovum AG and the Fraunhofer IZI

Since 2011, Sonovum AG has been working with the Fraunhofer IZI to develop a new diagnostic procedure which aims to improve the diagnosis of stroke and brain hemorrhage. The goal is to develop a mobile diagnosis device which will detect stroke at an early stage and would therefore be highly effective in reducing the severe consequential damage caused by this widespread illness. The project is being funded through the Sächsische Aufbaubank (Saxon Development Bank, SAB) using means provided by the European Regional Development Fund (ERDF) and the Free State of Saxony.

On March 20, 2013, the Saxon Minister of State for Science and the Arts, Professor Sabine Freifrau von Schorlemer, visited both institutes as part of a workshop in order to see how the project was panning out. The partners explained how the project had progressed so far and highlighted important milestones in the development of the company. The visit was rounded off by a tour of the laboratory.



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FRAUNHOFER IZI AND THE YOUTH INITIATIVE "JUGEND FORSCHT"

"Jugend forscht" is a national competition open to young researchers which fosters exceptional performance and talent in math, IT, natural sciences and technology. The Fraunhofer IZI supported two winning projects as part of the competition in 2013.

March 19 – 20, 2013: "Colors under the skin – a good idea?"

Supported by the Fraunhofer IZI's Extracorporeal Immunomodulation unit in Rostock, a group of school pupils from the Christopherus-Gymnasium Rostock grammar school took the title in the Biology category of the national competition "Jugend forscht". The title of their work was "Colors under the skin – a good idea?" and dealt with the cytotoxicity of tattoo inks. The school group looked at the general impact of tattoo inks on the human body, rather than just on the skin. Based on their investigations, the group came to the conclusion that, besides a high exposure to cadmium and iron, some of the inks examined contained non-regulated color pigments which could lead to health problems. It was also determined that human immune cells (granulocytes) become partially or completely dysfunctional in their main function, phagocytosis, when they come into contact with the inks.

May 30 – June 2, 2013: "Development of a new molecular-biology method to detect pathogenic germs"

Together with the Fraunhofer IZI's Nanotechnology unit, Nora Liebmann won the "Jugend forscht" regional competition in Saxony in the Biology category. She received a special prize in the subsequent national competition: an invitation to the Nobel Prize award ceremony in Stockholm. Nora has focused her work on analysis methods for dangerous germs and noted that the current procedures either take a long time or are involve high costs. In the search for a more convenient solution, she experimented with so-called beads – minuscule magnetic particles which can bind certain bacteria using antibodies. The young researcher replaced expensive antibodies with peptides which capture E. coli bacteria. She detected the bound germs using a molecular-biology procedure. Her peptide alternative is inexpensive and can quickly detect germs, although the applied methods first have to become more sensitive before they can be used in practice.

1 *Nobel Prize award ceremony 2013*

2 *Nora Liebmann at the Nobel Prize award ceremony in Stockholm*

April 25, 2013: Girls'Day at the Fraunhofer IZI

Girls'Day in Germany took place for the 13th time on April 25, 2013. Girls'Day is an annual day of action which aims to encourage women and girls in particular to take up technical and scientific careers. The Fraunhofer IZI took part in 2013 for the second time. 15 female participants were given the opportunity to gain an insight into the scientific world of work during a spot of practical training in the laboratory, while at the same time finding out about the research topics covered by the Fraunhofer IZI as well as career opportunities within the Fraunhofer-Gesellschaft.

By taking part in Girls'Day, the Fraunhofer IZI aimed to mainly address girls in the upper stage of grammar school in the hope that more women will fill executive roles in scientific enterprises in future.

The next Girls'Day will be held on March 27, 2014.

September 27 – 28, 2013: Rostock, ISAD 14th International Symposium on Albumin Dialysis

The 14th International Symposium on Albumin Dialysis took place from September 27 to 28, in Rostock/Warnemünde. The event was primarily organized by the forum for liver dialysis "FORUM LEBERDIALYSE e.V." in close coordination with the Fraunhofer IZI EXIM department. The symposium brought together around 100 internationally established experts to discuss the latest findings from the fields of extracorporeal blood purification as well as liver support systems. Discussions focused on the clinical aptitude of new and optimized systems and on findings from various studies.

1 *Girls'Day*
2 *International Symposium on Albumin Dialysis*

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October 24, 2013: Fraunhofer Life Science Symposium

As part of the World Conference on Regenerative Medicine, the annual Fraunhofer Life Science Symposium (FSL) took place on October 24, 2013 at the Congress Center in Leipzig. This year's event concentrated on technologies for the automated manufacture of cells and cell products. We were able to welcome David J Williams from Loughborough University as our keynote speaker. The event was organized by the Fraunhofer IZI together with the Fraunhofer Institute for Manufacturing Engineering and Automation IPA. Around 100 conference guests took in the presentations. The next Fraunhofer Life Science Symposium will be held from October 9 – 10, 2014 at the Fraunhofer IZI in Leipzig, where the focus will be on medical stem cell products.

December 4, 2013: German-Korean Symposium

On December 4, 2013, in collaboration with the Chonnam National University Hospital Hwasun (CNUHH), the Fraunhofer IZI organized a joint German-Korean Symposium in Leipzig. The two establishments have already been working together since 2010 and a number of researchers from both partner institutions have taken part in exchanges during this time, which allowed them to contribute their knowledge and experience to the respective guest country and expand on their own skills. In an annual, joint symposium, representatives from both project partners come together to bring one another up to date on the state of research on the one hand, and to initiate new cooperations on the other.

Colleagues from both Leipzig and Korea presented their research work in the fields of "Molecular Genetics of Diseases", "Imaging", "Therapeutics" and "Vaccine Therapeutics". Alongside this, a comprehensive cultural program was arranged for the Korean guests, which gave everyone plenty of time to discuss future cooperation projects. The next joint symposium will take place in Korea in 2014.

1 *Guests at the German-Korean Symposium on December 4, 2013 in Leipzig*

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December 11, 2013: topping out ceremony for the second extension building

Following the completion of the second construction phase of the Fraunhofer IZI at the end of 2012 and its official inauguration on January 23, 2013, work on the institute's third construction phase had already begun by spring 2013. It only took a few months to put together the shell, which meant that the size and shape of the entire building ensemble on the former trade fair grounds could already be made out by the end of 2013. The completion of the carcass work was celebrated in good tradition with a small topping out ceremony on December 11, 2013. This gave the institute and the building users the opportunity to thank the involved companies and guilds for the speedy and straightforward construction phase. Despite frosty temperatures, planners, builders and institute staff met at the construction site to toast the symbolic final nail in the roof truss after the topping out speech. The institute's "second daughter cell" is planned to be finished by spring 2015 and will house new laboratories, offices and seminar space as well as an additional GMP facility and a technical center, all covering an area of 3,200 m².

1 *The topping-out wreath marks the completion of the second extension building shell.*

LOOKING TO 2014

March 27, 2014
Girls'Day 2014
www.girls-day.de

April 9–12, 2014
8th International Symposium on Neuroprotection and Neurorepair
www.neurorepair-2014.de

June 27, 2014
Long Night of the Sciences in Leipzig
www.wissenschaftsnacht-leipzig.de

July 4, 2014
Long Night of the Sciences in Halle
www.wissenschaftsnacht-halle.de

October 9–10, 2014
Fraunhofer Life Science Symposium
www.fs-leipzig.com

October 20–22, 2014
ESBB Conference
www.esbb.org

SCIENTIFIC PRESENCE

CONVENTIONS AND CONFERENCES

11th International Conference on Alzheimer's and Parkinson's Diseases, AD / PD™ (oral presentation), March 6 – 10, 2013, Florence, Italy

14th International Symposium on Albumin Dialysis (ISAD) (attendee), October 27 – 29, 2013, Rostock, Germany

22nd European Stroke Conference (attendee), May 28 – 31, 2013, London, UK

28th TBI Winter Seminar (attendee), February 10 – 17, 2013, Bled, Slowenia

4th Annual Symposium "Physics of Cancer" (attendee), September 24 – 27, 2013, Leipzig, Germany

4th Industrial Cell Technologies (oral presentation), September 12 – 13, 2013, Lübeck, Germany

4th Research workshop held by Rostock University of Medicine (oral presentation), November 22 – 23, 2013, Rostock, Germany

9th International Nanotechnology Conference on Communication and Cooperation (attendee), May 14 – 17, 2013, Berlin, Germany

9th National industry conference on health management (oral presentation / attendee), July 10 – 11, 2013, Rostock-Warnemünde, Germany

AAIC – Alzheimer's Association International Conference (oral presentation), July 13 – 18, 2013, Boston, USA

Biomarker Conference (attendee), November 26 – 27, 2013, Munich, Germany

Biotechnika (attendee), October 9, 2013, Hannover, Germany

Cachexia Conference (attendee), December 9 – 11, 2013, Kobe, Japan

COST (attendee), October 8 – 9, 2013, Leipzig, Germany

CTAD – Clinical Trails in Alzheimer's Disease (attendee), November 14 – 17, 2013, San Diego, USA

Drug Biochemistry Symposium to Mark the 80th Birthday of Prof. Dr. A. Barth (oral presentation / attendee), December 9, 2013, Halle / Saale, Germany

EMBO | EMBL Symposium "The Non-Coding Genome" (attendee), October 9 – 12, 2013, Heidelberg, Germany

ESBB Conference (oral presentation), October 9 – 11, 2013, Verona, Italy

FNANO (attendee), April 15 – 18, 2013, Snowbird, USA

Fraunhofer IZI – Mc Master Collaborative Research Meeting (oral presentation), September 25, 2013, Hamilton, Canada

Fraunhofer Symposium "Netzwert" (oral presentation / attendee), December 3 – 4, 2013, Munich, Germany

GANI MED annual conference (oral presentation / attendee), September 16 – 17, 2013, Greifswald, Germany

German Biotechnology Conference (oral presentation), May 14 – 15, 2013, Stuttgart, Germany

German Conference on Cheminformatics (attendee), November 10 – 12, 2013, Fulda, Germany

Heinrich-Warner Symposium "The Prostate Cancer Genome" (oral presentation / attendee), June 13 – 15, 2013, Hamburg, Germany

Informa Cell Therapy Manufacturing Congress (attendee), December 4 – 5, 2013, Brussels, Belgium

Interactive Workshop of PharmaMar (oral presentation / attendee), November 7 – 8, 2013, Madrid, Spain

iPET.4 (oral presentation), September 7, 2013, Ostrau, Germany

ISMB ECCB (attendee), July 19 – 23, 2013, Berlin, Germany

LRMN & The NanoKTN event (oral presentation), January 30, 2013, London, UK

Medica (attendee), November 24 – 25, 2013, Düsseldorf, Germany

Med Logistica (oral presentation), May 15 – 16, 2013, Leipzig, Germany

Qualified Person Education Course (attendee), October 1 – 2, 2013, Barcelona, Spain

SENS6 Conference (oral presentation), September 3 – 7, 2013, Cambridge, UK

Society for Neuroscience Meeting 2013 (oral presentation / attendee), November 9 – 13, 2013, San Diego, USA

SPIE Photonics West 2013 (attendee), February 2 – 7, 2013, San Francisco, USA

Stroke symposium (attendee), March 1 – 2, 2013, Berlin, Germany

Symposium: modern vaccination strategies (attendee), June 10, 2013, Berlin, Germany

The 12th Annual Human Proteome Organization World Congress, 2013 (attendee), September 14 – 18, 2013, Yokohama, Japan

The Product is the Process – Is it? (attendee), November 12, 2013, Berlin, Germany

World Conference on Regenerative Medicine (attendee), October 23 – 25, 2013, Leipzig, Germany

World Congress of Neurology (attendee), September 21 – 26 2013, Vienna, Austria

RESEARCH PARTNERS

AIT Austrian Institute of Technology, Health & Environment Department , Vienna, Austria

Biomedical Primate Research Centre, Department of Virology, Rijkswijk, The Netherlands

Brigham & Women's Hospital, Harvard Medical School, CND, Boston, USA

Caritas Hospital St. Josef, University of Regensburg, Clinic for Gynecology and Obstetrics, Regensburg, Germany

Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin, Medical Department, Division of Hematology, Onkology, Berlin, Germany

Chonnam National University, Hwasun Hospital, Gwangju, South Korea

CIDEIM Centro Internacional de Entrenamiento e Investigaciones Medicas, Cali, Colombia

Clinic St. Georg gGmbH, Robert Koch Clinic, Leipzig, Germany

Ernst Moritz Arndt University Greifswald, University Hospital, Institute for Immunology and Transfusion Medicine, Greifswald, Germany

Federal Institute for Risk Assessment (BfR), Product Safety & Center for the Documentation and Evaluation of Alternatives to Animal Experiments, Berlin, Germany

Flensburg University of Applied Science, Department of Biotechnology and Process Engineering, Flensburg, Germany

Fraunhofer Institute for Applied Information Technology FIT, Sankt Augustin, Germany

Fraunhofer Institute for Biomedical Engineering IBMT, St. Ingbert, Germany

Fraunhofer Institute for Electron Beam and Plasma Technology FEP, Dresden, Germany

Fraunhofer Institute for Electronic Nano Systems ENAS, Chemnitz, Germany

Fraunhofer Institute for Interfacial Engineering and Biotechnology, Stuttgart, Germany

Fraunhofer Institute for Ceramic Technologies and Systems IKTS, Dresden, 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 Mechanics of Materials IWM, Business unit Biological and macromolecular materials, Halle/Saale, Germany

Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Aachen, Germany

Fraunhofer Institute for Process Engineering and Packaging IVV, Freising, Germany

Fraunhofer Institute for Reliability and Microintegration IZM, Berlin, Germany

Fraunhofer Institute for Toxicology and Experimental Medicine ITEM, Hannover, Germany

Friedrich-Alexander-Universität Erlangen-Nürnberg, Franz Penzoldt Center, Erlangen, Germany

Furtwangen University, Faculty for Manufacturing Systems Engineering and Process Engineering, Villingen-Schwenningen, Germany

Ghent University, Faculty of Veterinary Sciences, Laboratory for Gene Therapy, Ghent, Belgium

Helmholtz Centre for Environmental Research – UFZ, Department Proteomics | Department Environmental Immunology, Leipzig, Germany

Helmholtz-Zentrum Dresden Rossendorf, Department Radiopharmaceutical and Chemical Biology (FWPB), Dresden, Germany

Heart Center Leipzig GmbH, Clinic for Cardiology, Leipzig, Germany

Leipzig University of Applied Science, Faculty of Electrical Engineering and Information Technology, Leipzig, Germany

Karolinska Institut, Department of Medicine, Solna, Stockholm, Sweden

Leibniz Institute of Photonic Technology, Department of Nanobiophotonics, Jena, Germany

Liverpool School of Tropical Medicine, Centre for Applied Health Research & Delivery, Liverpool, UK

Ludwig Maximilians University Munich, German Center for Neurodegenerative Diseases | Fakulty of Physics, Chair for Experimental Physics: Soft Condensed Matter and Biophysics, Munich, Germany

Martin Luther University Halle-Wittenberg, Department of Anatomy and Cell Biology, Halle/Saale, Germany

Max Planck Institute for Human Cognitive and Brain Sciences, Neurophysics, Leipzig, Germany

McMaster University, Department of Engineering Physics | McMaster Immunology Research Centre, Hamilton, Canada

Otto von Guericke University Magdeburg, Institute of Process Engineering, Magdeburg, Germany

Radboud University Nijmegen, Faculty of Science, Institute for Molecules and Materilas, Bio-organic Chemistry, Nijmegen, The Netherlands

Research Center Borstel, Leibniz Center for Medicine and Biosciences, Borstel, Germany

Riken Brain Science Institute, Proteolytic Neuroscience, Tokyo, Japan

Saxon State Office for Environment, Agriculture and Geology, Animal Breeding, Köllitsch, Germany

Seoul National University, NANO Systems Institute, Seoul, South Korea

St. Elisabeth Clinic Leipzig, Department for Urology | Senology/Breast Center, Leipzig, Germany

Stanford University, School of Medicine, Department of Neurosurgery, Stanford, USA

University of California, Los Angeles, Department of Neurology, Geffen School of Medicine, Los Angeles, USA

University of Bergen, Clinical Science, Bergen, Norwegen

Leipzig University, Center for Biotechnology and Biomedicine | Faculty of Physics and Earth Sciences, Soft Matter Physics Division | Clinic and Polyclinic for Diagnostic and Interventional Radiology | Clinic and Polyclinic for Neurology | Faculty of Medicine, Medical Experimental Center | Paul Flechsig Institute | Translational Centre for Regenerative Medicine (TRM) | Translational Centre for Regenerative Medicine (TRM) Leipzig, Research Area CELLT – Cell Therapies for Repair and Replacement | University Gynecological Clinic | Faculty for Veterinary Medicine | Faculty for Veterinary Medicine, Large Animal Clinic for Theriogenology and Ambulatory Services | Faculty for Veterinary Medicine, Animal Surgery Clinic | Faculty for Veterinary Medicine, Bird and Reptile Clinic | Faculty for Veterinary Medicine, Institute for Veterinary Anatomy | Faculty of Veterinary Medicine, Institute for Veterinary Pathology, Leipzig, Germany

University of Rostock, Faculty for Medicine, Institute for Transfusion Medicine, Rostock, Germany

University of Salzburg, Priority Program BioScience and Health, Salzburg, Austria

University of Cologne, Faculty of Mathematics and Natural Sciences, Department for Chemistry, Institute for Biochemistry, Cologne, Germany

University of Zurich, Vetsuisse Faculty, Institute for Laboratory Animals, Zurich, Switzerland

University Hospital Carl Gustav Carus , Department for Neuropathology | Urology, Dresden, Germany

University Clinic Leipzig, Department for Imaging and Radiation Medicine, Division of Neuroradiology | Department for Imaging and Radiation Medicine, Clinic and Polyclinic for Nuclear Medicine | Department for Imaging and Radiation Medicine, Clinic for Radiation Therapy and Radiooncology | Department for Diagnostics, Institute for Clinical Immunology and Transfusion Medicine | Department for Diagnostics, Institute for Medical Microbiology and Infection Epidemiology | Department for Diagnostics, Institute for Pathology | Department for Diagnostics, Institute for Virology | Department for Internal Medicine, Neurology and Dermatology, Division for Hematology and Internal Oncology | Department for Internal Medicine, Neurology and Dermatology, Clinic and Polyclinic for Dermatology, Venerology and Allergology | Department for Internal Medicine, Neurology and Dermatology, Clinic and Polyclinic for Gastroenterology and Rheumatology | Department of Ophthalmology, Leipzig, Germany

University Clinic Regensburg, Institute for Clinical Chemistry and Laboratory Medicine | Clinic and Polyclinic for Internal Medicine I, Division Rheumatology and Clinical Immunology, Regensburg, Germany

University Clinic Rostock, public-law institution, Clinic and Polyclinic for Radiation Therapy | Center for Internal Medicine, Clinic II, Department for Gastroenterology, Rostock, Germany

University Hospital Münster, Clinic and Polyclinic for Neurology, Münster, Germany

ADVANCED VOCATIONAL TRAINING

University Medical Center of the Johannes Gutenberg University Mainz, Institute for Microscopic Anatomy and Neurobiology, Research Group Molecular Imaging and Optogenetics, Mainz, Germany

University of Adelaide, Adelaide Centre for Neuroscience Research, Adelaide, Australia

University of Belgrade, Center for Laser Microscopy, Belgrade, Serbia

University of California, Pharmacy & Pharmaceutical Sciences, San Diego, USA

University of Eastern Finland, Institute of Clinical Medicine/ Neurology, Kuopio, Finland

University of Nottingham, School of Medicine, Division of Oncology, Nottingham, UK

University of Padova, Department of Molecular Medicine, Padua, Italy

University of Thessaloniki, Medical School, Thessaloniki, Greece

University of Virginia, Department of Biology, Charlottesville, USA

Uppsala University, Engineering Sciences, Uppsala, Sweden

Urological Practice & Study Institute Dr. Schulze, Markkleeberg, Germany

Washington University, School of Medicine, Division of Infectious Diseases, St. Louis, USA

Yale University, Yale School of Medicine, Department of Molecular Biophysics and Biochemistry, New Haven, USA

Acquisition seminar: basic sales / marketing training, SMILE – Selbst Management Initiative LEipzig, Leipzig, Germany

Äkta training course, GE Healthcare, Munich, Germany

Update on technical X-ray knowledge, State Institute for Personal Dosimetry and Radiation Protection Training Mecklenburg-Vorpommern, Berlin, Germany

Blood, blood products and components – quality and safety, Concept Heidelberg GmbH, Vienna, Austria

Case-based introduction to biostatistics, coursera.org, online

Digital PCR seminar, Bio-Rad Laboratories GmbH, Leipzig, Germany

Documentation obligations in the GxP environment, World Courier (Deutschland) GmbH, Leipzig, Germany

Flow cytometry, applications and optimization, eBioscience, Leipzig, Germany

Freezing processes and long-term storage of cells – demands on quality and technical solutions, Askion GmbH, Leipzig, Germany

ELISA technology: establishment, optimization and validation, Klinkner & Partner GmbH, Munich, Germany

Employability and leadership skills for young saxon researchers, Leipzig University, Research Academy, Leipzig, Germany

Endotoxin determination in the QC laboratory – from classic (LAL) to innovative (rFC) methods, Lonza Cologne GmbH, Cologne, Germany

Training for specialists in internal medicine, intensive medicine section and examination as a medical specialist, Leipzig University Hospital, public-law institution, Leipzig, Germany

Advanced training course for specialists, Leipzig University, Faculty of Medicine, Leipzig, Germany

Specialist in molecular biology (TÜV), "Gläsernes Labor" learning lab, BBB Management GmbH Campus Berlin-Buch, Berlin, Germany

FACS-course FC500, Beckman Coulter GmbH, Krefeld, Germany

FACS-course MoFlow, Beckman Coulter GmbH, Leipzig, Germany

FACS advanced training software by eBioscience, Leipzig University, Interdisciplinary Centre for Clinical Research, Leipzig, Germany

FELASA C, Berliner Fortbildungen, Berlin, Germany

Funding for science based on the example of the DFG, Leipzig University, ELSYS Skills School, Leipzig, Germany

Fit4 Horizon2020, Martin Luther University Halle-Wittenberg, Department for Media and Communication, Halle, Germany

Leadership and management in the laboratory, Klinkner & Partner GmbH, Saarbrücken, Germany

Functional cell-based assays, Ibidi GmbH, Rostock, Germany

Hazardous goods training, World Courier (Deutschland) GmbH, Berlin, Germany

Device briefing for FC500, Beckman Coulter GmbH, Krefeld, Germany

Device qualification and computer validation, Karlsruhe Institute of Technology, Center for Advanced Technological and Environmental Training, Karlsruhe, Germany

Device training for Navios, Beckman Coulter GmbH, Krefeld, Germany

GLP training: QA in in vivo trials, SOP management in the GLP area, Vivotecnia Research, Leipzig, Germany

GMP basic training, PTS Training Service, Leipzig, Germany

Good Distribution Practice, World Courier (Deutschland) GmbH, Leipzig, Germany

Grant writing, Kompetenzschule ELSYS, Leipzig, Germany

Foundations of flow cytometry, eBioscience, Leipzig, Germany

Foundations and application of flow cytometry, Becton Dickinson GmbH, Rostock, Germany

Autumn symposium, OSHO/ Leipzig, Faculty of Medicine, Halle, Germany

Illumina User Group Meeting, Illumina Inc., Heidelberg, Germany

Innovations for individualized medicine, Federal Ministry of Education and Research, Berlin, Germany

Innovative application with Nucleofector technology: knockdown, screening and reprogramming, Lonza Cologne GmbH, Leipzig, Germany

Communication and leadership, Klinkner & Partner GmbH, Potsdam, Germany

Course on laboratory animals 1–3, Leipzig University, Faculty of Medicine, Medical Experimental Center, Leipzig, Germany

Course for study leaders: "Concept and conduct of clinical trials", Leipzig University, Clinical Trial Centre, Leipzig, Germany

LaTeX course, Leipzig University, Leipzig, Germany

MACS Flow Day – Flow cytometry basics, Miltenyi Biotec GmbH, Leipzig, Germany

Mathematical Biostatistics, coursera.org, online

MoFlo XDP training, Beckman Coulter GmbH, Leipzig, Germany

Molecular biology training, Instag GmbH, Zwenkau, Germany

Seminar on molecular biology methods, Thermo Fisher Scientific, Leipzig, Germany

Microbiological ambient monitoring (S6), Concept Heidelberg GmbH, Heidelberg, Germany

Network Analysis in Systems Biology, coursera.org, online

New GDP guidelines, Elpro Messtechnik GmbH, Frankfurt, Germany

Particle College, Reinraum-Akademie GmbH, Leipzig, Germany

Investigator training – foundations and practice of clinical trials, KKS-Netzwerk, Rostock, Germany

Real Time PCR, Bio & SELL e. K., Heidelberg, Germany

Social media for scientists, Fraunhofer Institute for Cell Therapy and Immunology IZI, Leipzig, Germany

The doctoral degree as a project: Managing complex research projects, Leipzig University, Research Academy, Leipzig, Germany

Troubleshooting in cell culture, PromoCell GmbH, Rostock, Germany

Validation and verification of analysis procedures, Klinkner & Partner GmbH, Koblenz, Germany

EVALUATOR ACTIVITIES

Responsibilities of the head of manufacturing, Concept Heidelberg GmbH, Frankfurt, Germany

Air safety training, FR8 solutions GmbH, Bad Salzungen, Germany

Specialized advanced training in internal medicine, Leipzig University Hospital, public-law institution, Leipzig, Germany

Specialized advanced training in veterinary medicine for laboratory animals, Chamber of Veterinarians, Leipzig, Germany

"Conscious language" workshop, 115th Conference of the Central German Society of Pneumology and Thorax Surgery, Gera, Germany

"Speech and presentation" workshop, SMILE – Selbst Management Initiative LEipzig, Leipzig, Germany

Writing and publishing a research paper, Graduierten-akademie Universität Rostock, Rostock, Germany

Seminar on cell viability tests, proliferation tests and toxicity tests, PromoCell GmbH, Heidelberg, Germany

Acta Cryst. D: Biol. Crystallography, Dr. Stephan Schilling

Advanced Materials, Dr. David M. Smith

Alzheimer's Association, Prof. Dr. Hans-Ulrich Demuth

American Journal of Physiology, Prof. Dr. Hans-Ulrich Demuth

Special learning module at Wilhelm-Ostwald-Gymnasium Leipzig, Dr. Stephan Fricke

Biochimica Biophysica Acta, Prof. Dr. Hans-Ulrich Demuth

Biological Chemistry, Prof. Dr. Hans-Ulrich Demuth

BMC Infectious Diseases, PD Dr. Sebastian Ulbert

Federal Ministry of Education and Research: FHprofUnt research funding initiative and next-generation engineers, Prof. Dr. Hans-Ulrich Demuth

Chemical Science, Dr. David M. Smith

Clinical and Experimental Immunology, Dr. Stephan Fricke, (Reviewer)

Clinical and Experimental Vaccine Research, PD Dr. Sebastian Ulbert (Editorial Board)

Clinical Microbiology and Infection, PD Dr. Sebastian Ulbert

German Research Foundation Prof. Dr. Hans-Ulrich Demuth

Drug Design Reviews, Prof. Dr. Hans-Ulrich Demuth (Editorial Advisory Board Member)

European Journal of Biochemistry, Prof. Dr. Hans-Ulrich Demuth

FEBS-Letters, Prof. Dr. Hans-Ulrich Demuth

Future Drugs – Expert Reviews Vaccines, Dr. Jörg Lehmann

Future Science Group, Dr. David M. Smith

High-Tech Gründerfonds Bonn on the Steinbeis Transfer Center, Prof. Dr. Hans-Ulrich Demuth

Innovation management – life science and medical technology, technology transfer and law at the Helmholtz Association, Prof. Dr. Hans-Ulrich Demuth

Journals (Bioinformatics, RNA, Cancer Research, JBCB, TIBI), Dr. Kristin Reiche

Journal of Alzheimer's Disease, Dr. Stephan Schilling

Journal of Alzheimer's Disease, Prof. Dr. Hans-Ulrich Demuth (Handling Editor)

Journal of American Chemical Society, Prof. Dr. Hans-Ulrich Demuth

Journal of Biological Chemistry, Prof. Dr. Hans-Ulrich Demuth

Journal of Chromatography B, Prof. Dr. Hans-Ulrich Demuth

Journal of Environmental Research and Public Health, PD Dr. Sebastian Ulbert

Journal of Neurochemistry, Prof. Dr. Hans-Ulrich Demuth

Journal of Physical Chemistry, Dr. David M. Smith

Life Sciences, Prof. Dr. Hans-Ulrich Demuth

Methods, Dr. David M. Smith

Microchimica Acta, Dr. Dirk Kuhlmeier

Neurodegenerative Disorders, Prof. Dr. Hans-Ulrich Demuth

PloS One, Dr. Gesa Weise

PloS One, Dr. Stephan Schilling

Psychiatric Genetics, Dr. Holger Kirsten

Soft Matter, Dr. David M. Smith

TEACHING ACTIVITIES

The International Journal of Neuroscience, Angiogenesis, Plos One, Stroke, Dr. Daniel-Christoph Wagner

The Open Veterinary Science Journal, Dr. Jörg Lehmann (Editorial Board)

Veterinary Immunology and Immunopathology, Dr. Jörg Lehmann

Vector-Borne and Zoonotic Diseases, PD Dr. Sebastian Ulbert

Viruses, PD Dr. Sebastian Ulbert

Weston Garfield Family Funds, Prof. Dr. Hans-Ulrich Demuth

World Conference on Regenerative Medicine: Abstracts, Dr. Alexander Kranz

World Conference on Regenerative Medicine: Abstracts, Dr. David M. Smith

World Conference on Regenerative Medicine, Christopher Oelkrug

World Conference on Regenerative Medicine, Dr. Stephan Fricke (Chair)

Magazine for gerontology and geriatrics, Dr. Claire Fabian

Helmholtz Centre for Environmental Research (UFZ):
Analysis of high-throughput molecular biological data using R and Bioconductor (course), Dr. Kristin Reiche, Dr. Jörg Hackermüller;
Introduction to statistical programming with R (course), Dr. Kristin Reiche, Dr. Jörg Hackermüller

Anhalt University of Applied Sciences:
Protein biotechnology (lecture), Prof. Dr. Hans-Ulrich Demuth, Dr. Jens-Ulrich Rahfeld

Leipzig University of Applied Sciences:
Microfluidics and dosing systems (lecture), Dr. Dirk Kuhlmeier

Martin Luther University Halle-Wittenberg:
Molecular biotechnology (lecture), Dr. Stephan Schilling;
Production of hosts and vectors (practical training), Dr. Stephan Schilling

Leipzig University:
Acute leukemia (course), Dr. Stephan Fricke;
Active ingredient analytics – practical training (course), Dr. Mirko Buchholz;
Introduction to clinical medicine (course), Dr. Stephan Fricke;
History of natural sciences with focus on pharmacy (lecture), Dr. Mirko Buchholz;
Basics of immunology (lecture), Dr. Jörg Lehmann;
Core lecture on immunology (lecture), Prof. Dr. Frank Emmrich;
Immunological methods (lecture), Dr. Jörg Lehmann;
Immunological practical training for medical practitioners (practical training), Dr. Stephan Fricke, Nadja Hilger;
Vaccination and vaccines (lecture), Dr. Sebastian Ulbert;
Infectiology and immunology (problem-oriented learning), Prof. Dr. Frank Emmrich;
Infectiology and immunology (course), Dr. Alexander Kranz;
Practical training in the laboratory, virology module (practical training), Dr. Sebastian Ulbert;
lymphomas (course), Dr. Stephan Fricke;
Medical biotechnology (lecture), Dr. Franziska Lange;
Medical biotechnology/ regenerative medicine (lecture), Prof. Dr. Frank Emmrich;
Monoclonal antibodies – manufacturing and application (lecture), Dr. Jörg Lehmann;
POL-1 Infectiology and immunology (problem-oriented learning), Dr. Franziska Lange;
Polyvalent course on laboratory animals (course), Margarethe Köberle;
Prevention and health promotion (lecture), Prof. Dr. Frank Emmrich;
QSB tissue typing (seminar), Dr. Stephan Fricke, Nadja Hilger;
QSB tissue typing (seminar), Dr. Stephan Fricke, Felix Schmidt;
QSB transfusion medicine (seminar), Christopher Oelkrug;
QSB environmental medicine I (seminar), Margarethe Köberle;
QSB environmental medicine II (seminar), Veronika Storbeck;
Response mechanisms in organic chemistry (seminar), Dr. Daniel Ramsbeck;
Mosquito-transferred virus diseases (lecture), Dr. Sebastian Ulbert;
Terminology for pharmacists (seminar), Dr. Daniel Ramsbeck;
Vector-transferred virus infections (lecture), Dr. Sebastian Ulbert;
Virology for human medicine specialists on the topic of vaccination (course), Dr. Sebastian Ulbert

University of Rostock:
Subject-specific accompanying seminar on internal medicine (seminar), Prof. Dr. Steffen Mitzner; Internal medicine I (lecture), Objective structured clinical examinations (seminar), Prof. Dr. Steffen Mitzner

ASSOCIATION MEMBERSHIPS

Alumni of the Faculty of Medicine at Leipzig University, Dr. Stephan Fricke

American Chemical Society (ACS), Dr. Mirko Buchholz, Prof. Dr. Hans-Ulrich Demuth, Dr. Daniel Ramsbeck

American Diabetes Association (ADA), Prof. Dr. Hans-Ulrich Demuth

American Heart Association, Dr. Alexander Deten, Dr. Alexander Kranz

American Society of Biochemistry and Molecular Biology (ASBMB), Dr. Claus Kerkhoff

American Stroke Association, Dr. Alexander Kranz

Study-group for experimental stem cell transplantation, Dr. Stephan Fricke

Doctors for Madagaskar, Prof. Dr. Frank Emmrich

Association for Cancer Immunotherapy (CIMT), Christopher Oelkrug

Australian Neuroscience Society, Dr. Antje Dreyer

biosaxony e.V., Prof. Dr. Frank Emmrich

German Society for Gerontology (DGfA), Dr. Alexandra Stolzing

German Society for Anesthesiology and Intensive Care (DGAI), PD Dr. Martin Sauer

German Society for Epidemiology (DGEpi), Dr. Holger Kirsten

German Society for Gerontologie and Geriatrics (DGGG), Dr. Alexandra Stolzing

German Society for Immunology (DGfI), Prof. Dr. Frank Emmrich, Dr. Stephan Fricke, Christiane Füldner, Dr. Franziska Lange, Dr. Jörg Lehmann, Christopher Oelkrug, Prof. Dr. Ulrich Sack, Dr. Ulla Schwertassek, Katharina Zoldan

German Society for Cardiology – Cardiovascular Research (DGK), Dr. Alexander Deten

German Society for Clinical Chemistry and Laboratory Medicine (DGKL), Prof. Dr. Frank Emmrich

German Society for Clinical Neurophysiology, Dr. Gesa Weise

German Society for Clinical Neurology, Dr. Gesa Weise

German Society for Parasitology, Peggy Bodammer

German Society for Regenerative Medicine (GRM), Prof. Dr. Frank Emmrich, Dr. Stephan Fricke, Dr. Alexandra Stolzing

German Society for Stem Cell Research (GSZ), Prof. Dr. Frank Emmrich

German Society for Virology (GfV), PD Dr. Sebastian Ulbert

German Interdisciplinary Association for Intensive Care and Emergency Medical Aid (DIVI), Prof. Dr. Steffen Mitzner

German Morbus Crohn / Colitis Ulcerosa Association DCCV, Peggy Bodammer

Deutsche Pharmazeutische Gesellschaft, Dr. Mirko Buchholz, Dr. Daniel Ramsbeck

German Physiologic Society (DPG), Dr. Alexander Deten

German Sepsis Society (DSG), Prof. Dr. Steffen Mitzner, PD Dr. Martin Sauer

German Society for Clinical Chemistry and Laboratory Medicine (DGKL), Prof. Dr. Ulrich Sack

German Society for Veterinary Medicine (DVG), Anne Kühlmann

German Zoologic Society (DZG), Dr. Gustavo Makert dos Santos

German Ethics Council, Prof. Dr. Frank Emmrich

German Association of University Professors and Lecturers (DHV), Dr. Alexander Deten

European WNV Research Platform, PD Dr. Sebastian Ulbert

European Autoimmunity Standardization Initiative (EASI), Prof. Dr. Ulrich Sack

European Macrophage and Dendritic Cell Society (EMDS), Dr. Claus Kerkhoff

European Molecular Biology Laboratory (EMBL) Alumni Association, PD Dr. Sebastian Ulbert

European Renal Association / European Dialysis and Transplantation Association (ERA-EDTA), Prof. Dr. Steffen Mitzner

European Society for Advances to Study Diabetes (EASD), Prof. Dr. Hans-Ulrich Demuth

European Society for Artificial Organs (ESAO), Prof. Dr. Steffen Mitzner

European Society for Clinical Cell Analysis (ESCCA), Prof. Dr. Ulrich Sack

Förderverein für Medizinische Ausbildung (FörMA e. V.), Prof. Dr. Frank Emmrich

Friends of Veterinary Medicine Faculty of the Leipzig University, Dr. Jörg Lehmann

German QP Association, Kati Kebbel, Dr. Gerno Schmiedeknecht

German Society of Biological Chemistry and Molecular Biology (GBM), Prof. Dr. Hans-Ulrich Demuth

German Society of Mass Spectrometry (DGMS), Prof. Dr. Hans-Ulrich Demuth

German Stem Cell Network (GSCN), Prof. Dr. Frank Emmrich

German Chemical Society (GDCh), Dr. Michael Szardenings

Society for Biochemistry and Molecular Biology (GBM), Dr. Holger Cynis, Prof. Dr. Hans-Ulrich Demuth, Prof. Dr. Frank Emmrich, Dr. Claus Kerkhoff, Dr. Stephan Schilling, Dr. Michael Szardenings

Society for Chemical Engineering and Biotechnology (DECHEMA), Prof. Dr. Frank Emmrich

Society for Nephrology (GfN) (GfN), Prof. Dr. Steffen Mitzner

Society for Laboratory Animals (GV-SOLAS), Dr. Jörg Lehmann

Association for the Advancement of Immune Diagnostics (GfID), Prof. Dr. Ulrich Sack

GLP Commission, Prof. Dr. Ulrich Sack

International Dyslexia Association, Dr. Arndt Wilcke

International Proteolysis Society (IPS), Prof. Dr. Hans-Ulrich Demuth

International Society for Heart Research (ISHR), Dr. Alexander Deten

International Union for the Study of Social Insects, Dr. Gustavo Makert dos Santos

Leipzig Initiative for Biotechnology, Prof. Dr. Frank Emmrich

Leipziger Stiftung für Innovation und Technologietransfer (Leipzig foundation for innovation and technology transfer), Prof. Dr. Frank Emmrich

MEDICA German Society for Interdisciplinary Medicine, Prof. Dr. Frank Emmrich

National Research Platform for Zoonoses, PD Dr. Sebastian Ulbert

German Neuroscience Society (NWG), Dr. Anna Leichsenring

New York Academy of Sciences, Prof. Dr. Hans-Ulrich Demuth

Protein Society (PS), Prof. Dr. Hans-Ulrich Demuth

Society for Neuroscience (SfN), Dr. Holger Cynis, Prof. Dr. Hans-Ulrich Demuth, Dr. Alexander Kranz, Dr. Björn Nitzsche, Dr. Daniel-Christoph Wagner, Dr. Vilia Zeisig

Verein zur Förderung der Gesundheitswirtschaft in der Region Leipzig e. V. (Association for the promotion of health management in the Leipzig region) (VfG), Prof. Dr. Frank Emmrich

Verein zur Förderung Regenerativer Medizin e. V. (Association for the promotion of regenerative medicine), Prof. Dr. Frank Emmrich

Vereinigung von Freunden und Förderern der Universität Leipzig e. V., Prof. Dr. Frank Emmrich

Central Committee for Animal Protection, Directorate Leipzig, Dr. Jörg Lehmann

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Bach C, Hilger N, Köberle M, Przybylski S, Marschner A, Lange F, Fricke S, Jülke H, Burkhardt J. **Graft versus host disease: an overview of murine in vivo disease models.** 12th Leipzig Research Festival for Life Science 2013, 19.12.2013, Leipzig, Germany.

Bäcker I, Flemmig J, Leichsenring A, Lange F, Arnhold J. **Perspective analysis of myeloperoxidase activity in a chronic rat model of rheumatoid arthritis.** World Conference on Regenerative Medicine, 23.–25.10.2013, Leipzig, Germany.

Bäcker I, Leichsenring A, Flemmig J, Arnhold J, Lange F. **Beneficial effects of epigallocatechin gallate from green tea in a rat model of chronic rheumatoid arthritis.** 12th Leipzig Research Festival for Life Science 2013, 19.12.2013, Leipzig, Germany.

Bäcker I, Leichsenring A, Lange F, Isensee T, Guntermann H, Sack U. **Anti-inflammatory effects of NRI-1006 in the CIA mouse model of rheumatoid arthritis.** 43th Annual Meeting of German Society for Immunology, 11.–14.9.2013, Mainz, Germany.

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Zoldan K, Kreß J, Möllmer T, Frank F, Fueldner C, Knauer J, Fuerll M, Kauffold J, Starke A, Fischer R, Bergfeld U, Pache S, Lehmann J. **Milk haptoglobin – immunological biomarker for health monitoring of dairy cows (poster).** 43. Jahrestagung der Deutschen Gesellschaft für Immunologie DGfI, 11.–14.9.2013, Mainz, Germany.

Zoldan K, Kreß J, Möllmer T, Frank F, Fueldner C, Knauer J, Fuerll M, Kauffold J, Starke A, Fischer R, Bergfeld U, Pache S, Lehmann J. **Haptoglobin in milk – potential biomarker of inflammation for health monitoring of dairy cows (oral presentation).** Annual Meeting »Veterinärimmunologischer Arbeitskreis« (VIA) of the German Society for Immunology (DGfI), 5.–6.4.2013, Vienna, Austria.

Cynis H, Schilling S, Demuth HU. **Glutaminyl cyclases.** In: Handbook of biologically active peptides/ed. Abba Kastin. 2nd Edition, Elsevier 2013, S. 1736–1742.

Dreyer AY, Lobsien D, Pösel C, Hoffmann KT, Nitzsche B, Findeisen M, Stroh A, Boltze J. **Tracking of autologous VSOP-labeled mesenchymal stem cells in the sheep brain using 3.0 T MRI.** In: Jolkkonen J, Walczak P: Cell-Based Therapies in Stroke. Springer, 2013, S. 105–125.

Reinhardt J, Flory E, Büttel I, Schröder C, Fricke S, Vucinic V, Cross M, Niederwieser D. **MSCs: Clinical Applications and European Regulatory Aspects.** In: Mesenchymal stromal cells : biology and clinical applications/ed. by P. Hematti. Springer, 2013, S. 355–364, DOI 10.1007/978-1-4614-5711-4_18, ISBN 978-1-4614-5710-7, Online ISBN 978-1-4614-5711-4. Stem cell biology and regenerative medicine.

Smith D. **Programmed nucleic acid assembly for nanomedicines.** In: Jonathan P Wong (Hrsg.): Nucleic acid-based drugs. London: Future Science, 2013, S. 116–131. doi: 10.4155/ebo.13.438.

OTHER PUBLICATIONS

Ehlert U. **Dye Transfer Assay – Zell-Zell-Kommunikation via gap junctions und ihre Bedeutung in der Tumorimmuntherapie.** MTA Dialog. 14 (2013), 3, S. 244–247.

Graubaum K. **Kurz und schmerzlos.** Unternehmen Region 2/2013, S. 10–12, Herausgeber BMBF, Referat »Regionale Innovationsinitiativen; Neue Länder«, 11055 Berlin.

Kuhlmeier D, Gärtig C. **Mit PCR der Parodontitis auf der Spur: mikrobielle Diagnostic.** Biospektrum 19 (2013), 1, S. 160–162. doi: 10.1007/s12268-013-0289-x.

van Ackeren J, Fricke S. **Vielversprechende Stammzelltherapie bei Leukämie.** FORSCHUNG KOMPAKT 04 | 2013 || Thema 3.

GRADUATION (CLASS OF 2013)

Didwischus, Nadine. **Investigations into the migration pattern of immune cells in a humanized mouse chimera.** Leipzig University, Master's degree.

Dithmer, Sophie. **Characterization of three mouse models in order to induce experimental allergic asthma.** Martin Luther University of Halle-Wittenberg, Master's degree.

Kohlschmidt, Janine. **Influence of benzo[a]pyrene on the functional properties of murine bone marrow macrophages.** Anhalt Köthen University of Applied Sciences, Master's degree.

Krauel, Alexander. **Clarification of the mode of action and identification of the clinically relevant effects of colocynth and sage-based herbal medicinal products.** Leipzig University, Diploma.

Küntzel, Carolin. **Inactivation of viruses for vaccine development.** Ernst Abbe University of Applied Sciences Jena, Master's degree.

Leitschuh, Nadine. **Development of a lab-on-a-chip system to identify and quantify the main germs relevant to periodontitis.** Fulda University of Applied Sciences, Bachelor's degree.

Manthe, Kristina. **Tumoricidal effect of frog secretion and synthetic frog peptides on murine and human melanoma cells.** Emden/Leer University of Applied Sciences, Bachelor's degree.

Matuschek, Brian. **Investigation into the functionality of T cells in the humanized NSG mouse.** Leipzig University, Master's degree.

Naumann, Andreas. **Production and characterization of recombinant proteins for targeted application in the direct detection or enrichment of nucleic acids.** Leipzig University, Doctorate degree.

Schicht, Gerda. **Investigation of the immunomodulatory effects of the granulocyte colony-stimulating factor (G-CSF) on the splenocyte Th1/Th2 immune response following a stroke.** Zittau/Görlitz University of Applied Sciences, Bachelor's degree.

Stößel, Maria. **Integration of a magnetic particle based analysis method to demonstrate sepsis-related pathogens in a lab-on-a-chip system.** Leibniz University Hanover, Master's degree.

Thomsen, Maren. **Extracorporeal sepsis treatment using cascade plasma therapy: influence of different pre-fill fluids on survival and clinical course in a pig sepsis model of gram-positive sepsis.** University of Rostock, Doctorate degree.

Wilcke, Arndt. **Genetic investigations into dyslexia.** Leipzig University, Doctorate degree.

Wilhelm, Martin. **Studies to improve cell adhesion to surfaces and scaffolds.** University of Applied Sciences Mittweida, Bachelor's degree.

Zeisig, Vilia. **Establishment of a hypoxia tracer to illustrate penumbra in a positive contrast using PET and creation of a method to improve penumbral blood flow in an ovine animal model for stroke research.** Leipzig University, Doctorate degree.

PRIZES

Poster prize awarded by the German Society for Nuclear Medicine to Dr. Vilia Zeisig from the Clinic-oriented Therapy Assessment unit on the topic "[15O]H2O-PET to monitor the CBF effect of inhaled nitric oxide in an ovine stroke model".

Poster prize awarded at the 12th Research Festival 2013 held by Leipzig University to Dr. Holger Kirsten from the Cognitive Genetics unit on the topic "Genome-wide analysis of the genetic regulation of the human transcriptome identifies novel regulators and corroborates the regulatory relevance of non-protein coding loci/Analysis of gene expression applicable to the functional relevance of 'dyslexia genes'/eQTL".

"Jugend forscht" competition for young researchers, held by the "Jugend forscht" foundation, won by Nora Liebmann from the Nanotechnology unit on the topic "Development of a new molecular biological method to detect pathogenic germs".

PATENTS

The patent portfolio of the Fraunhofer IZI currently holds 27 patent families which are available for use in cooperation projects as well as for direct commercialization and licensing.

Fraunhofer IZI holds patents 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
- Procedure for isolating homogeneous tumor stem cell populations
- New procedure for preventing Graft-versus-Host-Disease (GvHD)
- Method for immobilizing cells on surfaces
- Procedure for diagnosing dyslexia
- Procedure for the cryopreservation of cells and tissues
- Methods for ascertaining liver function and regeneration

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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. In the same manner, the expenses of about 11 million Euros for construction and equipment of the extension building were covered. The plot of land is provided by the City of Leipzig in hereditary leasehold and free of charge.

European Union

Bundesministerium für Bildung und Forschung

Freistaat Sachsen

LEIPZIG

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:

- Dr. Henrich Guntermann (Chair) (Nuvo Research Inc., CEO)
- Dr. Knut Bartl (emeritus Roche Diagnostics GmbH, CSO Werk Penzberg)
- Dr. Annerose Beck (Saxon State Ministry of Science and the Arts (SMWK), Deputy Head of National-Regional Research Centers Administration)
- Prof. Dr. Andreas H. Guse (University Hospital Hamburg-Eppendorf, Vice-Dean for Teaching)
- Prof. Dr. Hans-Martin Jäck (University Hospital Erlangen, Head of the Molecular Immunology Department, President of the German Society for Immunology)
- Prof. Dr. Friedrich-Wilhelm Mohr (Heart Center Leipzig GmbH – University Hospital – Medical Director)
- Prof. Dr. Gerhard Oechtering (Leipzig University, Director of the Small Animal Hospital)
- Dr. Kai Pinkernell (Miltenyi Biotec GmbH, Head of Research in Clinical Development)
- Prof. Dr. Andreas Pinkwart (HHL Leipzig Graduate School of Management, Dean)
- Prof. Dr. Thomas Skutella (University of Heidelberg, Head of Department at the Institute for Anatomy and Cell Biology)
- Dr. Christina de Wit (Federal Ministry of Education and Research (BMBF), Desk Officer for Health Care Management)
- Klaus Berka* (Analytik Jena AG, CEO)

*Member of the advisory board as of 2014

The Chairman of the advisory board, Dr. Albrecht Schmidt, resigned from the board in 2013. The entire institute would like to thank Dr. Schmidt for his many years of commitment, for his constructive input and for supporting us with his extensive economic knowledge and experience. As his successor, Dr. Henrich Guntermann (Nuvo Research Inc.) was unanimously elected Chairman of the advisory board.

FRAUNHOFER-GESELLSCHAFT

THE FRAUNHOFER-GESELLSCHAFT IN PROFILE

Research of practical utility lies at the heart of all activities pursued by the Fraunhofer-Gesellschaft. Founded in 1949, the research organization undertakes applied research that drives economic development and serves the wider benefit of society. Its services are solicited by customers and contractual partners in industry, the service sector and public administration.

At present, the Fraunhofer-Gesellschaft maintains 67 institutes and independent research units. The majority of the more than 23,000 staff are qualified scientists and engineers, who work with an annual research budget of 2 billion euros. Of this sum, more than 1.7 billion euros is generated through contract research. More than 70 percent of the Fraunhofer-Gesellschaft's contract research revenue is derived from contracts with industry and from publicly financed research projects. Almost 30 percent is contributed by the German federal and state governments in the form of base funding, enabling the institutes to work ahead on solutions to problems that will not become acutely relevant to industry and society until five or ten years from now.

Affiliated international research centers and representative offices provide contact with the regions of greatest importance to present and future scientific progress and economic development.

With its clearly defined mission of application-oriented research and its focus on key technologies of relevance to the future, the Fraunhofer-Gesellschaft plays a prominent role in the German and European innovation process. Applied research has a knock-on effect that extends beyond the direct benefits perceived by the customer: Through their research and development work, the Fraunhofer Institutes help to reinforce the competitive strength of the economy in their local region, and throughout Germany and Europe. They do so by promoting innovation, strengthening the technological base, improving the acceptance of new technologies, and helping to train the urgently needed future generation of scientists and engineers.

As an employer, the Fraunhofer-Gesellschaft offers its staff the opportunity to develop the professional and personal skills that will allow them to take up positions of responsibility within their institute, at universities, in industry and in society. Students who choose to work on projects at the Fraunhofer Institutes have excellent prospects of starting and developing a career in industry by virtue of the practical training and experience they have acquired.

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.

Executive board (in December 2013)

Prof. Dr. Reimund Neugebauer, President of the Fraunhofer-Gesellschaft, Corporate Management
Prof. (Univ. Stellenbosch) Dr. Alfred Gossner, Finance, Controlling (incl. Business Administration, Purchasing and Real Estate), Information Technology
Dr. Alexander Kurz, Personnel and Legal Affairs

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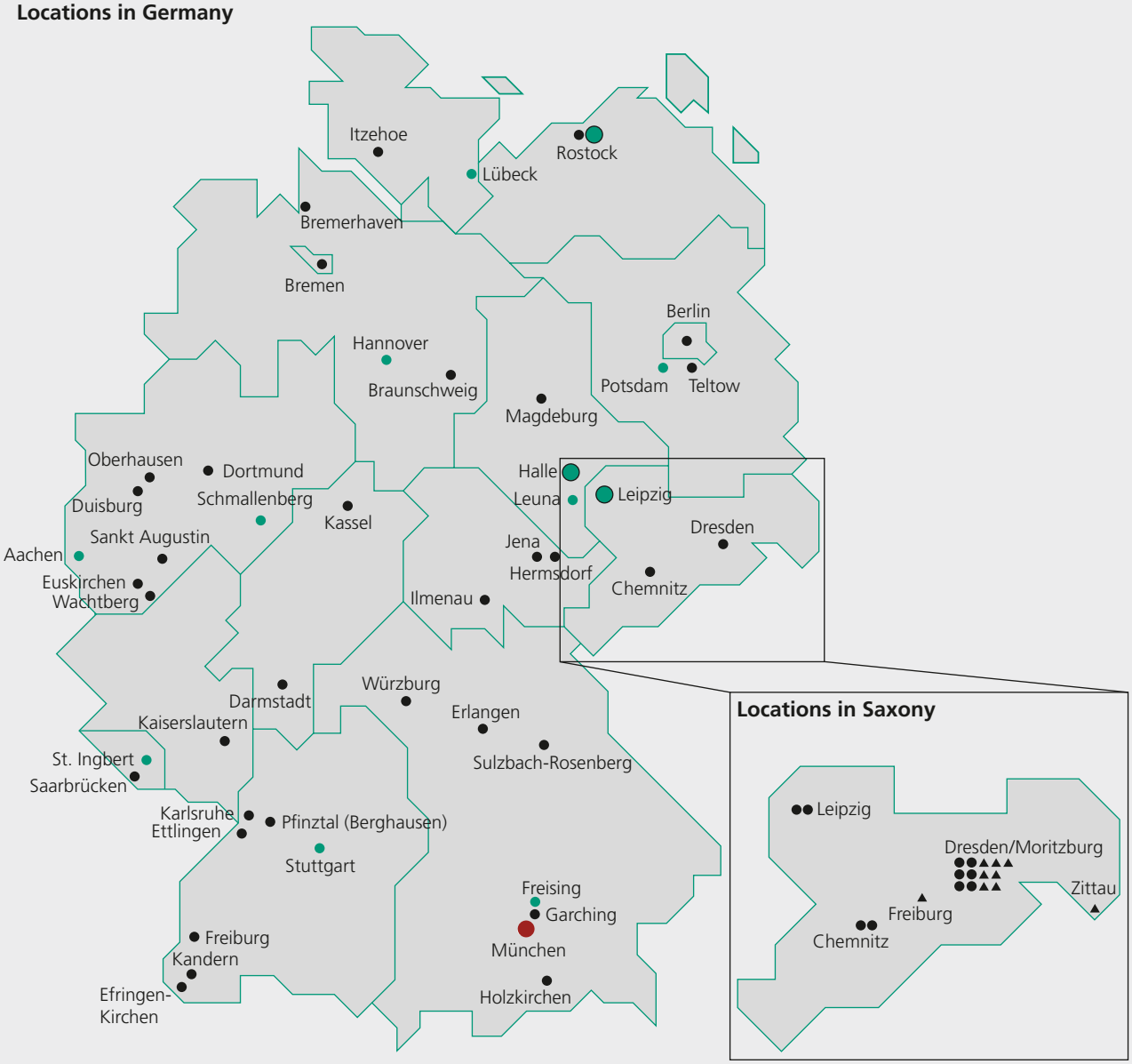

- Fraunhofer Institute
- Head office of Fraunhofer-Gesellschaft, Munich
- Location of institute of the FraunhoferGroup for Life Sciences
- Fraunhofer IZI

- Institute/independent research establishment
- Other location

FRAUNHOFER GROUP FOR LIFE SCIENCES

The Fraunhofer Group for Life Sciences was founded in 2001 to strengthen the fields of life sciences, biomedicine and biotechnology. It currently comprises seven institutes.

In terms of expanding research revenue as well as business spin-offs, the Fraunhofer Group for Life Sciences is one of the Fraunhofer-Gesellschaft's most dynamic areas of research.

Business units of the Fraunhofer Group for Life Sciences:

- Medical translational research and biomedical technology: The challenge of innovative diagnostics and personalized therapy
- Regenerative medicine: The challenge of qualified biobanking and controlled self-healing
- Healthy foods: The challenge of high consumer acceptance and disease prevention
- The new potential of biotechnology: The challenge to learn from nature for industrial exploitation
- Process, chemical, and herbicide safety: The challenge of environmental and consumer protection

The elected spokesman of the Fraunhofer Group for Life Sciences is Prof. Dr. Thomas Hirth, who heads the Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB in Stuttgart. Since 2008, Prof. Dr. Frank Emmrich (head of the Fraunhofer IZI) is deputy spokesman.

Institutes of the Fraunhofer Group for Life Sciences

- Fraunhofer Institute for Biomedical Engineering IBMT
- Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB
- Fraunhofer Institute for Molecular Biology and Applied Ecology IME
- Fraunhofer Institute for Toxicology and Experimental Medicine ITEM
- Fraunhofer Institute for Cell Therapy and Immunology IZI
- Fraunhofer Institute for Process Engineering and Packaging IVV
- Fraunhofer Research Institution for Marine Biotechnology EMB

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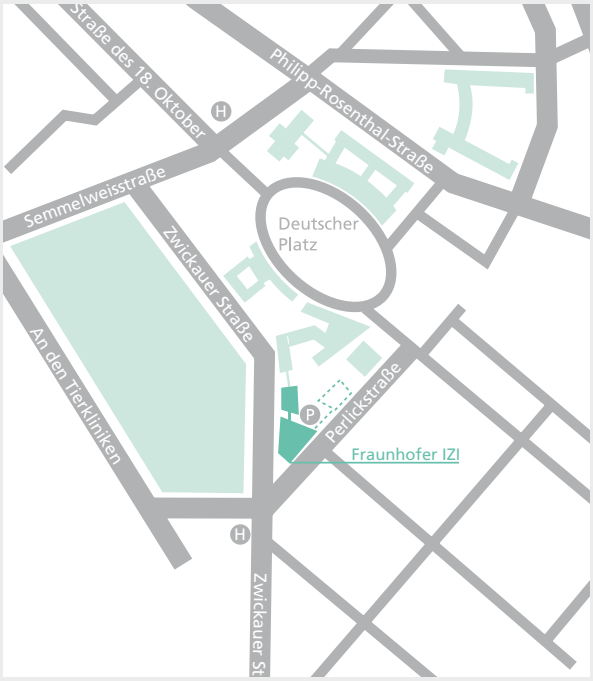

By car

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 Semmelweissstraße, 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 Semmelweissstraße, 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 S-Bahn train station is "Leipzig MDR" and all S-Bahn trains stop there (10 – 15 minute walk to the institute).

From the airport

From the airport take the urban train ("S-Bahn") to Leipzig Central Station ("Leipziger Hauptbahnhof"), then transfer to the number 16 tram in the direction of Lößnig and get off at the stop "An den Tierkliniken".

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Service Catalog (English)

Our service catalog gives you a comprehensive insight into the products and services offered by the Fraunhofer IZI. On the basis of a sorting according to work units you will quickly find your appropriate contact person at our institute and gain insight into reference projects or applicabilities.

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In combination with past years' issues, our current annual report gives you an insight into the structure of the Fraunhofer IZI, our services, important events and publications, offers, as well as selected project examples.

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An overview of interesting events held at the Fraunhofer IZI as well as further information on our institute can be found on our homepage www.izi.fraunhofer.de.

All our brochures and publications as well as current announcements made by the Fraunhofer IZI can be found on our homepage **www.izi.fraunhofer.de**. You can also mail to **presse@izi.fraunhofer.de** and order our brochures as hard copies.

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