



Fraunhofer Institut
Zelltherapie und
Immunologie

Annual Report 2008

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Annual Report 2008

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Dear Reader,

An interesting year lies behind us. A year in which we were able to increase the Institute income by 64.25 percent to 8.032 million euros. The most important event for the Institute last year was clearly the move into our finished new facility for which we organized a celebratory "Grand Opening" on the 27th of June 2008.

Through this move it has been possible for us to exchange the rented laboratories on the BIOCITY for excellently equipped laboratories, offices and conference rooms in our new building. The Fraunhofer IZI has gained its own persona through this move and our partners and customers now have an impressive collaborator who will carry out their research with state-of-the-art methods.

The building was handed-over on-time and within projected cost estimates, and our requests were completely taken into account. For this accomplishment special thanks from the Institute and its Director must be given to the architect and planners of the firm Heinle, Wischer & Partner and DERU as well as the construction department of the Fraunhofer Society and Mr. Weese and Mr. Bartl.

Our excellent young group leaders have continued the successes from the previous year. Dr. Johannes Boltze was the recipient of the impressive Hugo Geiger Prize for the work "Experimental Cell Therapy of Ischemic Stroke in the Rat through Use of the Stem Cell Population of the Human Umbilical Cord" which was granted by the German President at the annual Fraunhofer meeting in Berlin. Dr. Nicole zur Nieden accepted an offer for a tenure track position at the University of California, Riverside in the USA. The cooperation with California is particularly interesting through the extraordinary grant funding in the amount of 3 billion US dollars which is to be invested in California over the next 10 years.

As the coordinator for RNA-technologies at Fraunhofer IZI, Prof. Friedemann Horn is the driver behind one of the most important internal Fraunhofer consortiums, which is involved in the preparation of a Contractual Agreement between several Fraunhofers for the topic of Personalized Medicine. Following the competitive external evaluation of 66 new projects for the Translational Center for Regenerative Medicine in 2008 Dr. Wilke in cooperation with Mr. Kirsten has succeeded in winning first place from the jury for their molecular genetic project "Early Detection of Dyslexia".

In 2008 Fraunhofer IZI was active in acquisition of new technology areas and added a research group "Tumour Stem Cells" under the leadership of Dr. Ruschpler. The institute has also started to strengthen its expertise in medical technology. To this end, a group from Rostock was established which is specialized in extracorporeal immunomodulation systems and a second group was established in manufacture of nanofiber-woven scaffolds as cell carrier material.

In 2008 Fraunhofer IZI continued its activities in the organization of conferences and symposiums. Under the auspices of the Federal Minister Schavan together with the European Society for Vitality and Active Ageing e.V. (EVAAA) Fraunhofer IZI organized an Innovation Forum for occupational Health Mentoring. Fraunhofer IZI demonstrated a particularly lively interest in participating in the "Long Night of Science" in the Summer of Science in Leipzig. On this evening approximately 1000 citizens of Leipzig visited our new facility to take a look at the research themes, methodology, and goals. Based on a particularly innovative representation of their work, the research groups Boltze, Stolzing and zur Nieden were awarded the "Peoples Choice" award based on results gathered by a questionnaire.

Attendees of the grand opening of the Fraunhofer IZI building included the Federal minister for Transportation, Construction and City planning Mr. Tiefensee, as well as the Saxony State Minister for Science, Dr. Stange and the Mayor of Leipzig Dr. Jung. Furthermore, in the fall Fraunhofer IZI was visited by the newly elected minister president of the Free State of Saxony, Stanislaw Tillich as well as the State Minister Mr. Jurk and Ms. Claus.

For the upcoming year 2009 we are prepared, in spite of an uncertain business climate, to continue to intensify our efforts in investing in industry project acquisition and to bring to a positive end to the diverse larger projects that have been in preparation over a longer period. In the New Year we expect to be able to increasingly position ourselves as an attractive partner primarily through the acquisition of new technology in combination with established biological and medical competencies.

Leipzig, January 10, 2009



Prof. Dr. Frank Emmrich
Director



Profile

Outline

Aims

In the face of an aging society and an increase in chronic diseases, medicine is confronted with new challenges. The Fraunhofer-Institute for Cell Therapy and Immunology (IZI) has defined goals to embrace the promise of health and vitality even as the body ages.

In this aspect, the field of regenerative medicine has become increasingly important for the health care system. This novel biomedical research area has the potential to fight chronic diseases, autoimmune diseases and oncologic diseases, which lead often to irreversible damage of tissue and organs. The goal is to use cell therapies, tissue engineering or specific modulation of the immune system to treat degenerative diseases based on root causes rather than treating only the symptoms.

This goal can be reached through the stimulation of naturally regenerative processes of the body or by biological replacements via extracorporally engineered tissue.

General Theme:

Cell Therapy and Immunology

In its narrow sense, cell therapy means the transfer of cells to replace lost functions and even to adopt additional active tasks. It however also covers the treatment of cells through the repairing of deficiencies. Stem cells can be transferred in order to trigger tissue formation and repair. Cell therapy is hence related to immunology, which deals with cellular defense and monitoring mechanisms. Cell therapy techniques for the targeted strengthening, suppression and regeneration of the immune system, for example in order to stimulate the defense of degenerated cells or to suppress the undesired rejection of transplanted tissue, are

expected to be available soon. In addition, a prominent role is played by the development of immunomodulation techniques such as vaccination.

In line with its four fields of research, Fraunhofer IZI is currently divided into 15 thematically clustered groups. Fraunhofer IZI serves clients from the biotechnology industry, suppliers of medical equipment and pharmaceutical companies by performing intelligent, research-intensive services and carrying out development projects. The range of services offered by the institute includes market analyses, technical feasibility studies, and prototype development using human and animal cells and tissues, as well as the conclusive formulation of production and process technologies.

Field of Research:

Biotechniques – Models

In this area, Fraunhofer IZI develops technologies for the cultivation of tissues and cells outside the body (tissue engineering) in order to reconstruct tissues. This includes the development of custom bioreactors and the selection of specific material and surface properties. Fraunhofer IZI also has special expertise in developing techniques for the production of cell and tissue cultures as well as monoclonal antibodies. The institute's in-house production facilities are designed for the manufacture of clinical trial samples. Regarding the production of antibodies, Fraunhofer IZI is also skilled in the downstream processing of raw products. Cell and tissue models developed by our researchers can be used for testing, screening and the immunotoxicological examination of new drugs, cosmetics, food additives and industrial chemicals. The institute offers various small- and large-animal models for therapy development along the stages of the pharmaceutical development value chain.

Field of Research:

Immunology – Immunomodulation

This area includes the development of methods for the stimulation or suppression of the immune system. One key topic is improving the smooth acceptance of transplants by inducing specific tolerance. Fraunhofer IZI develops techniques to monitor immunoreactivity and to monitor unwanted responses such as GvHD (Graft versus Host Disease). It also develops vaccines on an innovative technology platform using plasmid DNA which are particularly safe, robust and inexpensive.

Field of Research:

Cell Therapy – Active Agents

In this area, cells are developed, cultivated and bred for therapeutic purposes. Fraunhofer IZI offers isolation and purification methods for cells from blood and tissue. It also develops special treatment techniques using T-cell clones and natural killer cells as well as vaccination strategies using dendritic cells for tumor treatment. One key area is cell therapy techniques for ischemic diseases such as stroke and myocardial infarction. Ongoing projects also include research into methods of preventing the degeneration and aging of cells. Furthermore, the institute explores "dormant" stem cell potential and derives new strategies for drugs able to control tissue growth and regeneration.

Field of Research:

Molecular Biology – Individualized Medicine

In the field of molecular biology, Fraunhofer IZI is working on a new technology platform which enables RNA molecules to be identified and ascertained for their potential to effect the intracellular control of signal processes. This provides indications for the development of new drugs. Furthermore, Fraunhofer IZI develops pharmacogenomic and protein-chemis-

try techniques for the identification of individual-specific differences from which particular disease susceptibility, sensitivity to certain methods of therapy and even the course of disease can be predicted.

History

The institute was officially founded in April 2005. Its first experimental work was conducted under a cooperation agreement with the University of Leipzig at the Max Bürger Research Center, before being continued and extended at Fraunhofer IZI's own laboratory at BIO CITY Leipzig in autumn 2005. This was only possible because 1,500 square meters of laboratory and office space at BIO CITY had been swiftly equipped thanks to smooth cooperation on the part of all those involved. In this context, it should be underlined that a newly devised clean room facility for GMP work in cell and tissue technology was planned, designed, built and validated within the space of just ten months, entering into operation when the first projects were performed there in summer 2006. On September 22, 2006, the cornerstone for the institute was laid right next door to BIO CITY for a 4,000 square meter building, which since April 2008 has offered exceptional working conditions.

Management

The structure and operation of Fraunhofer IZI are based on the successful experience of other Fraunhofer Institutes gathered over the years. The director of our institute is Prof. Dr. Frank Emmrich, who is also a professor at the University of Leipzig, where he has headed the Institute of Clinical Immunology and Transfusion Medicine since 1994. This dual position enables the efficient sharing of experience, not to mention the optimal supervision of undergraduate and doctoral dissertations, and provides an excellent basis for cooperation. Both a doctor and an immunologist, Prof. Emmrich spent 13



Press conference for the opening of the new Fraunhofer IZI building with Burkhard Jung, Prof. Dr. Emmrich and Wolfgang Tiefensee (f. l. t. r.; top left), inquisitive visitors at the Fraunhofer Life Science Symposium (bottom left) and exciting experiments at the "Long Night of Sciences" (right). More information on this topic on page 105.

Time Line

April 29, 2005	Institute is founded
October 2005	First laboratories at BIO CITY Leipzig (rehire)
June 2006	GMP facility opened
September 22, 2006	Foundation stone laid for the first wing of the new institute building
October 22 - 24, 2006	1st Fraunhofer Life Science Symposium »Cell Therapy and Immunology«
May 8, 2007	Visit by EU-commissioner responsible for Science and Research and the Saxon minister president
May 31, 2007	Roof-raising ceremony for the first wing of the new institute building
October 18 - 20, 2007	Organization of the 3rd World Congress on Regenerative Medicine by Fraunhofer IZI
October 18, 2007	2nd Fraunhofer Life Science Symposium »Tissue Regeneration in Veterinary Medicine«
June 27, 2008	Opening of the first wing of the new institute building
October 24 - 25, 2008	3rd Fraunhofer Life Science Symposium »Ischemia and Regeneration«



The new Fraunhofer IZI building.

years as both a researcher and department head at Max Planck Institutes in Freiburg and Erlangen. Over seven of these years he was a professor at the Friedrich Alexander University in Erlangen-Nuremberg.

Administration

The head of the institute is assisted by Patric Nitz – an administrator with an academic background in both management and the organization of staff training. He also holds an MBA from a British university and has several years experience managing departments and divisions in large organizational units in the public and private sectors.

Structure

In its current phase of development, Fraunhofer IZI is divided into 15 (increased to 17 in 2009) groups managed by their group leaders as business units. Their budgets are negotiated with the management of the institute every year – and the development and funding of each group largely depend on their success in attracting projects and contracts. Individual groups develop particular competencies which are made available as services not just externally, but also internally. The varied research competencies and services lead to synergies inside the institute and offer new perspectives to customers and research partners.

Facilities

On the premises and in laboratory space currently used, Fraunhofer IZI maintains standard laboratory facilities for biochemistry, molecular biology and cell biology, including a large inventory of equipment which is augmented by systems and instruments that are used cooperatively. For further details, please see the descriptions of the individual groups.

Animal Experiments

The first extension wing of the institute will include a department devoted to animal experiments. Experiments on animals are currently carried out in cooperation with the Faculty of Veterinary Medicine, the Faculty of Medicine and the Max Planck Institute for Evolutionary Anthropology. In addition, projects involving animal experiments have begun with the Faculty of Biology, Pharmacy and Psychology.

GMP Facility

One outstanding achievement in terms of precision and speed is the planning and completion of Fraunhofer IZI's multi-purpose GMP facility at the BIO CITY. It was planned, built and approved within the space of just ten months, enabling the first major contract to be started in summer 2006. It was also ensured that the new building would be connected via a bridge so that the GMP facility can continue to be used – hence granting planning certainty to all the partners involved.

Sponsors

In this context, Fraunhofer IZI would like to thank the European Union, the Federal Ministry of Education and Research, the Free State of Saxony, the city of Leipzig and the "Leipziger Stiftung für Innovation und Technologietransfer" for their financial support through the current development phase of the facility.



Financed by the European Union



Bundesministerium
für Bildung
und Forschung



Leipziger Stiftung
für Innovation und
Technologietransfer



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.

Dr. jur. Dr. h.c. oec. publ.

Albrecht Schmidt (Chair)

Bayerische Hypo- und Vereinsbank AG,
emeritus Chairman of the Supervisory Board

Dr. Annerose Beck

Saxon State Ministry of Science and the Arts (SMWK),
Deputy Head of National-Regional Research Centres Administration

Dr. Gabriele Hausdorf

Federal Ministry of Education and Research (BMBF),
Head of the Section of Health Research within the Department of Life Sciences

Dr. Michael Herschel

GlaxoSmithKline GmbH & Co. KG,
Head of Clinical Research

Dr. Eberhard Lampeter

VITA 34 AG,
Chairman

Prof. Dr. med. Gustav Steinhoff

University of Rostock,
Director of the Department of Cardiac Surgery

Prof. Dr. Hans Wolf

University of Regensburg,
Director of the Institute for Medical Microbiology and Hygiene

Perspectives

At the start of 2009, two new working groups will be established.

Prof. Dr. Steffen Mitzner, is a surgeon for internal medicine and leads a research group in extracorporeal detoxification at the University of Rostock. He has extensive expertise in the adaptation and novel development of therapeutic blood-exchange technology. This expertise represents an optimal fit with the current goals and concept of the Institute. In the framework of a project group, Prof. Mitzner brings the theme of extracorporeal immunomodulation to the Fraunhofer IZI.

The second new group at Fraunhofer IZI will be led by Dr. Gyeong-Man Kim. Dr. Kim was active as a physicist at the University of Halle-Wittenberg where he introduced the specialized manufacture of three-dimensional biodegradable tissue scaffolds.

Technology Coordinators

Currently the institute is focusing on its core competencies and in particular the identification of sustainable technologies. This allows the groups to establish strategic cooperation within the institute as well as within other Life Sciences Alliance members and with technology coordinators from other Fraunhofer Alliances. The established cooperation allows us to offer customers and partners particularly interesting service packages.

**Director of Fraunhofer IZI**

Prof. Dr. Frank Emmrich
 Phone: +49 (0) 341/355 36-9105
 frank.emmrich@izi.fraunhofer.de

**Administrative Head**

Patric Nitz
 Phone: +49 (0) 341/355 36-9200
 patric.nitz@izi.fraunhofer.de

**Project Service Team**

Dr. Wilhelm Gerdes
 Phone: +49 (0) 341/355 36-9300
 wilhelm.gerdes@izi.fraunhofer.de

Biotechniques – Models**Cell Engineering / GMP**

Dr. Gerno Schmiedeknecht
 Phone: +49 (0) 341/355 36-9705
 gerno.schmiedeknecht@izi.fraunhofer.de

**Cell Engineering / GLP**

Dr. Jörg Lehmann
 Phone: +49 (0) 341/355 36-1205
 joerg.lehmann@izi.fraunhofer.de

**Immunological Models**

Dr. Manja Kamprad
 Phone: +49 (0) 341/97 25-830
 manja.kamprad@izi.fraunhofer.de

Immunology – Immunomodulation**Vaccine Development**

Dr. Sebastian Ulbert (Laboratory)
 PD Dr. Matthias Giese (Head of Group)
 Phone: +49 (0) 341/355 36-2106
 sebastian.ulbert@izi.fraunhofer.de

**Immune Tolerance**

Dr. Stephan Fricke
 Phone: +49 (0) 341/355 36-2205
 stephan.fricke@izi.fraunhofer.de

**Virus-Host-Interaction**

Dr. Jörg Baumann
 Phone: +49 (0) 341/355 36-2505
 joerg.baumann@izi.fraunhofer.de
 Dr. Sabine Breun
 Phone: +49 (0) 341/355 36-2506
 sabine.breun@izi.fraunhofer.de

Cell Therapy – Active Agents



Immunotherapy – Oncology
Dr. Christoph Schimmelpfennig
 Phone: +49 (0) 341/355 36-3105
 christoph.schimmelpfennig@
 izi.fraunhofer.de



Neurorepair
 Dr. Johannes Boltze
 Phone: +49 (0) 341/97 25-814
 johannes.boltze@
 izi.fraunhofer.de



Stem Cell Technology
 Prof. Dr. Nicole zur Nieden
 Phone: +49 (0) 341/355 36-3305
 nicole.zurnieden@
 izi.fraunhofer.de



Stem Cell Biology
 Dr. Alexandra Stolzing
 Phone: +49 (0) 341/355 36-3405
 alexandra.stolzing@
 izi.fraunhofer.de



Cardiorepair
 Dr. Alexander Deten
 Phone: +49 (0) 341/355 36-3505
 alexander.deten@
 izi.fraunhofer.de



Tumor Stem Cells
 Dr. Peter Ruschpler
 Phone: +49 (0) 341/355 36-2605
 peter.ruschpler@izi.fraunhofer.de

Molecular Biology – Individualized Medicine



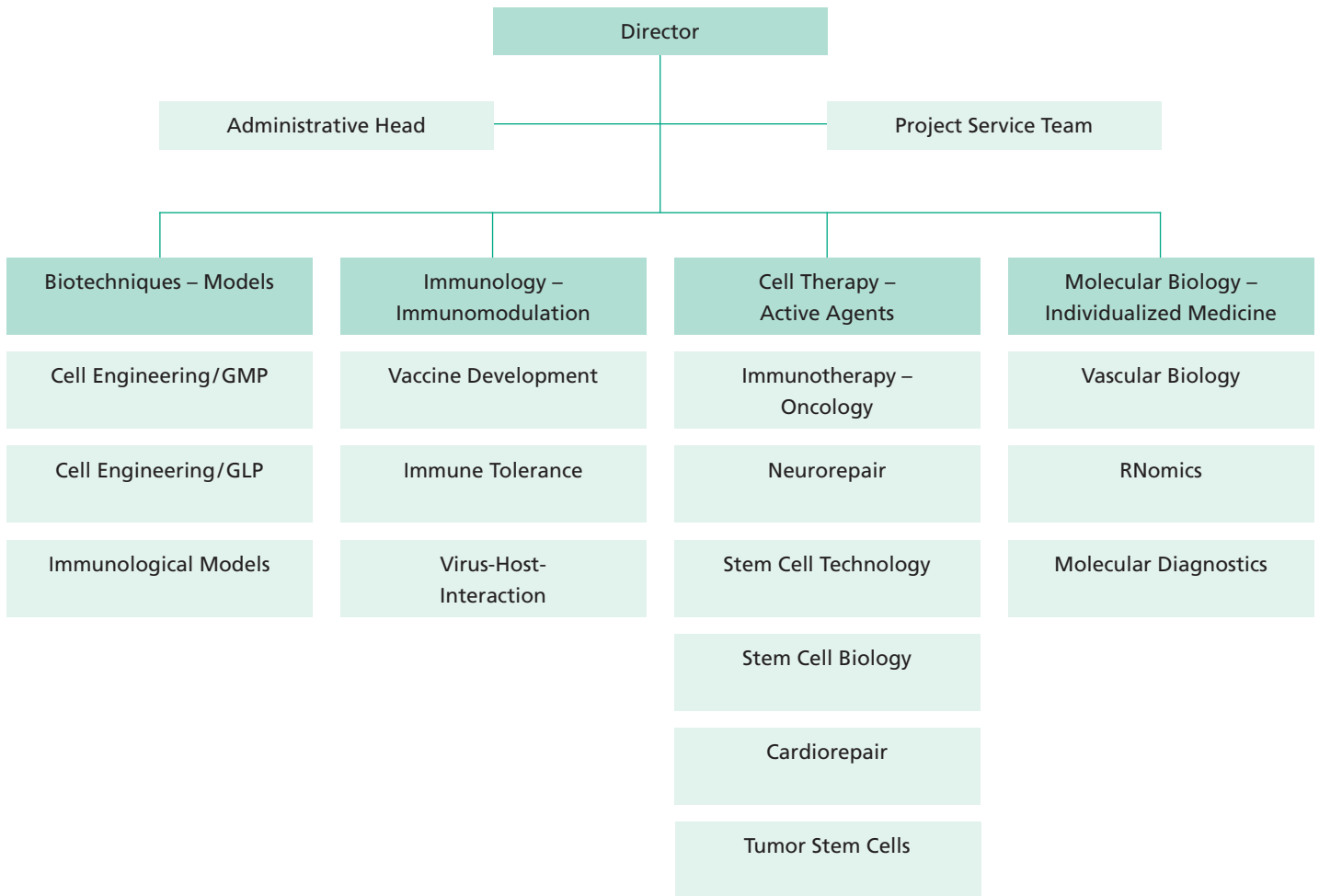
Vascular Biology
 Dr. Andreas Schubert
 Phone: +49 (0) 341/355 36-5105
 andreas.schubert@
 izi.fraunhofer.de



RNomics
 Dr. Jörg Hackermüller
 Phone: +49 (0) 341/355 36-5205
 joerg.hackermueller@
 izi.fraunhofer.de
 Dr. Antje Kretzschmar
 Phone: +49 (0) 341/355 36-5206
 antje.kretzschmar@
 izi.fraunhofer.de



Molecular Diagnostics
 Prof. Dr. Ulrich Sack
 Phone: +49 (0) 341/97 25-506
 ulrich.sack@izi.fraunhofer.de



Technology Coordinators



Antibody Technology

Dr. Gerno Schmiedeknecht
 Phone: +49 (0) 341/355 36-9705
 gerno.schmiedeknecht@
 izi.fraunhofer.de

Prof. Dr. Frank Emmrich
 Phone: + 49 (0) 341 / 355 36-9105
 frank.emmrich@izi.fraunhofer.de



RNA Technology

Prof. Dr. Friedemann Horn
 Phone: +49 (0) 341/355 36-5224
 friedemann.horn@
 izi.fraunhofer.de



Fraunhofer IZI in Figures



Contact

Patric Nitz
 Phone: +49 (0) 341/355 36-9200
 patric.nitz@izi.fraunhofer.de

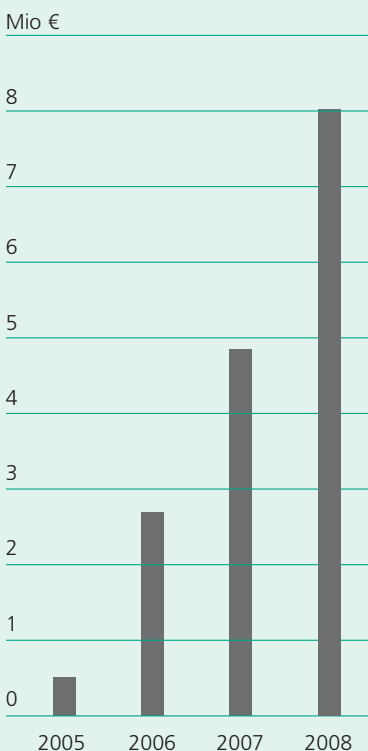
Budget

Generally speaking, the dynamic growth of the institute has continued in spite of the difficulties encountered in 2008. This in particular applied to the moving costs incurred during the move which was complicated by the high level of technically complex equipment in the central building. Furthermore the originally planned second building was unable to be completed in 2008. The planned building was to incorporate technically advanced equipment including an animal facility. The absence of this facility reduces our total revenue because we were unable to acquire third party contracts from parties who require such services.

According to Business Management theory, organizations are seen as goal-oriented decision-making systems with interpersonal divisions of labour. The division of labour requires restrictions on the freedom of action of the members of the organization through expectations circumscribing their behaviour. This has two dimensions, coordination and motivation. The coordination can ultimately arise from result from free choice (self-determination) or directives. Only the latter describes an organization.

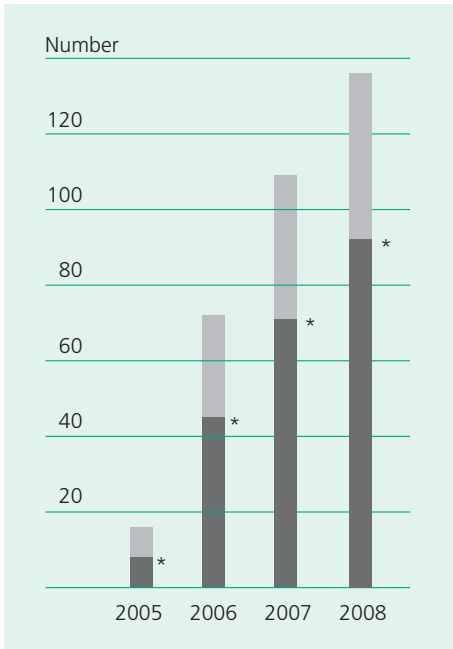
Overview of the Projects

	Number 2007	Volume 2007	Number 2008	Volume 2008
German national and regional government	8	3 032 000 €	8	5 417 954 €
EU	2	114 000 €	2	98 900 €
Industry Projects	18	605 000 €	23	943 600 €
Other	18	1 139 000 €	10	1 571 800 €
Total	46	4 890 000 €	43	8 032 254 €



■ budget of the institute

Budget



Employees (* percentage of women)



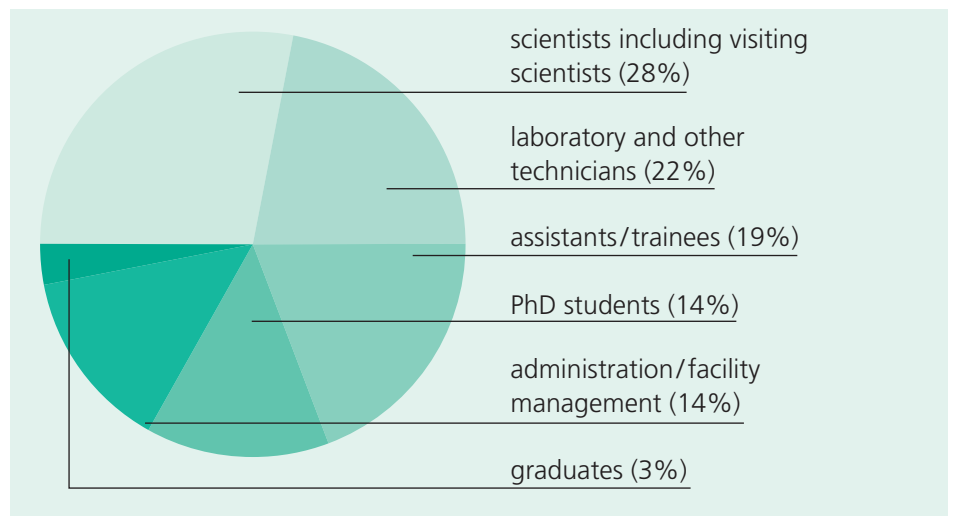
The administration: Patric Nitz, Mirko Reichardt, Detlef Klingler, Ute Schmidt, Falk Hoffmann, Daniel Becker, Cornelia Gruhle, Dirk Peisker, Anja Bochmann, Silvana Wiesel, Kristina Gentzsch.

Projects

The annual revenue could be increased from 4.890 Million euro in 2007 to 8.032 euro in 2008. This corresponds to a percent increase of 64 percent. The industry portion of this sum came to 12 percent of the total and 18 percent of the project revenues which demonstrates our increase in visibility in regards to our potential industry partners.

Human Resources

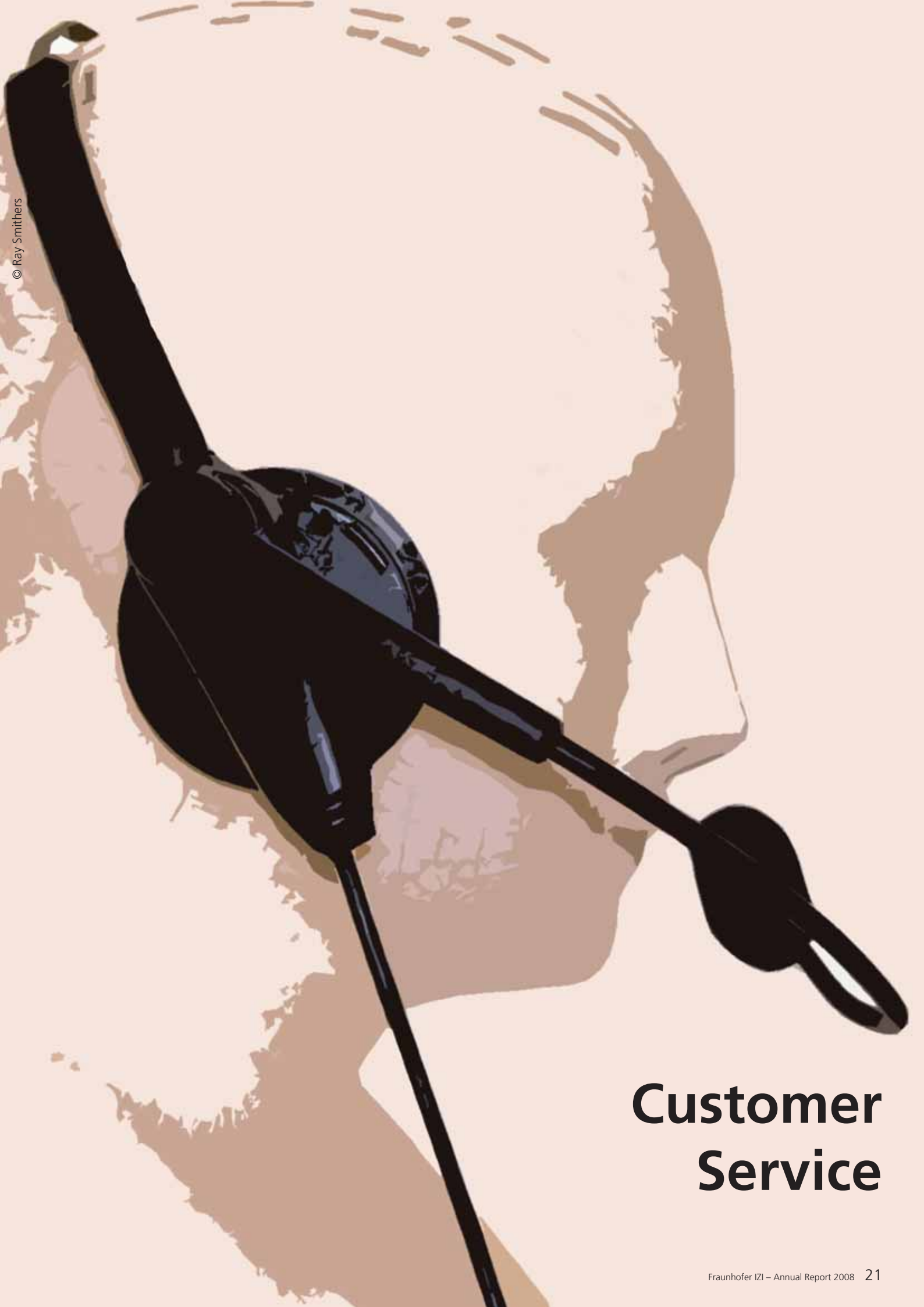
In 2008 new staff members were welcomed to Fraunhofer IZI. From the beginning to the end of 2008, the number of the colleagues increased by around 27 employees – from 109 to 136. Of these, 38 persons are active in the scientific area, and 19 persons are employed in the administration. Furthermore, 30 laboratory technicians as well as 4 Master’s graduates started work at Fraunhofer IZI in 2008. The number of staff, which are engaged short-term (interns, exchange scientists, trainees) or as doctoral candidates increased to 45. Of particular note is the high pro-



Workforce composition 2008

portion of female colleagues which as of 2008 increased to 92 which makes a total of 68 percent. This percentage makes Fraunhofer IZI one of the few institutes at which significantly more women work than men and this trend is expected to continue into the future. It is also notable that in 2008, two staff members took advantage of “Elternzeit” or parental leave, which is an

option following the birth of a child. The administration has significantly increased its professionalism itself through the acquiring of a specialized information manager.



Customer Service

Our Partners



Praxis PD Dr. Hoheisel
Leipzig



Alcyomics Ltd



MOLOGEN AG



SIEMENS



Research Contracts

The institutes of the Fraunhofer-Gesellschaft view themselves as professional research service providers. They render their service on the basis of contracts that define the content and deadlines as prescribed by the clients and that also reflect client's own needs and specifications. Of course, in the first phase, clients may be assured of confidentiality and non-disclosure of the contracted project.

Fraunhofer IZI has standardized contracts for phase 1, but is also prepared to make use of partner or client contracts that have been legally reviewed by the Fraunhofer-Gesellschaft. The contacts for this phase and in following phases of partnership are the members of the Project Service Team (PST) and/or the group leaders in whose field the agreed research services will occur.

In phase 2, the cornerstones of a contract are defined in a term sheet by the partner institutions. To effectively plan the targets, the contract timeframe and financial development are also sketched at this phase. The views of both parties regarding IP rights and utilization options will be agreed in essential points.

On this basis, the staff of Fraunhofer IZI prepares an offer or draft contract that will be discussed and negotiated in phase 4.

After review by the legal advisors of the partners, the agreement of the contract and its signing follows in phase 5.

Phase 1 – Confidentiality Agreement

Signing of a non-disclosure agreement. Original text may be from the partner or Fraunhofer-Gesellschaft.

Phase 2 – Term Sheet

Definition of the cornerstones between the partners (IP rights, utilization rights, contract timeframe, project plan, financial development).

Phase 3 – Offer

Drafting of the contract based on the project plan and cornerstones as defined in phase 2.

Phase 4 – Contract negotiation

Discussion and finalization of the contract by the partners.

Phase 5 – Contract agreement

Signing of the research contract after review and, if necessary, changes by the legal advisors of the partners.

Project Work

The key contact for clients is either the group leader or a member of the Business Development Team (PST). Both can supply the potential client with the necessary information. Assuming mutual interest in cooperation, Fraunhofer IZI has a non-disclosure agreement or a memorandum of understanding drawn up.

Project applications are painstakingly compiled for submission to public funding bodies and industry using the internal technology platforms at Fraunhofer IZI and the research groups' scientific competencies. In doing so, the team scrutinizes both the opportunities and the risks of projects and underpins applications by means of patent, literature and market research.

Afterwards, the partners compile a joint action plan, resulting in a project outline or application. This application provides the basis for subsequent contract negotiations conducted jointly between the partner, Fraunhofer IZI and the Fraunhofer-Gesellschaft. While the project is being carried out, the partner is kept abreast of its progress by the group leader or a team member at agreed regular intervals. Any scientific queries are addressed to the group leader. Following the completion of the project, a report will be written which is then submitted to the partner.



Project Service Team

Contact

Dr. Wilhelm Gerdes
Phone: +49 (0) 341/355 36-9300
wilhelm.gerdes@izi.fraunhofer.de

Services

- project acquisition
- project planning, coordination, management and marketing
- fundraising support
- public relations
- business development
- organizing and realization of scientific events
- planning and implementation of career development events

The identification and initial contact of potential cooperation partners and the evaluation of resulting projects are main charges of the PST.

Cooperation partners are often scientific research institutions and universities, but they are primarily businesses from pharmaceutical or biotechnology industry, medical technology, health economy or even the food industry. Conventions, symposia, congresses or direct contact are our main avenues of networking.

The PST or business development team at Fraunhofer IZI is of crucial importance to the initiation of projects. Team members support the individual groups every step of the way from evaluation to final reporting. In addition to many years of experience in scientific work, this includes a particular understanding of the way public authorities and commercial companies operate.

The primary function of this department is identifying and contacting potential cooperation partners. Contact is sometimes made through attending trade shows, conferences and conventions. Alternatively, new contacts are developed through existing partnerships that are continuously nurtured. In addition to national partnerships, the business development team is increasingly striving to set up international coopera-

tion. Apart from pinpointing potential cooperation partners, the team also is involved intensively with applying for funding for the mutual interest of its scientists and partners. It sifts through funding calls from the national and regional governments in Germany as well as throughout the European Union and forwards suitable ones to the relevant



The Project Service Team (f. l. t. r.): Kati Papenhagen, Kathrin Schmidt, Dr. Sonya Faber, Dr. Christian Zilch, Andreas Naumann, Jens Augustin, Susann Bachmann, Dr. Wilhelm Gerdes, Christina Kühn, Michaela Grahn.

groups at Fraunhofer IZI. Furthermore, the members of the business development team support the individual groups in drawing up project outlines and applications. The team forms the central interface of the institute and maintains close contact with grant officers at financing institutions in order to enable not just optimal communication, but also the successful controlling of project documentation.

Representing the institute and public relations is a further focus for the PST. The PST takes on the responsibility of representing the institute at the majority of public events and conventions, thereby relieving the research staff from this time commitment. Furthermore,

the team organizes internal career development and informative events. Starting in 2008 Fraunhofer IZI has offered its own seminar catalogue, which contains in addition to interdisciplinary seminars, scientific seminars taught by institute co-workers.

In the year 2006 the Fraunhofer Life Science symposium was created, and this event now takes place annually. The central topic rotates each year and the symposium continuously contributes to the extension of both scientific knowledge and industry contacts with Fraunhofer IZI research groups. In the coming year Fraunhofer IZI will additionally be considerably active in the organization of the World Conference on Regenerative Medicine in Leipzig. The meeting brings a high-level of international researchers together from across the globe, so that a forum

is created in which the current status of regenerative medicine research is reported on and discussed. The interdisciplinary meeting shines a light on various aspects of regenerative medicine, which extend from stem cell research through to biological materials and immunological topics as well as regulatory and legal guidelines.

www.fs-leipzig.com

www.wcrm-leipzig.com



Research and Services

Overview

The concrete products and services of the Fraunhofer IZI are shown below. For more information about the working groups see page 37.

A complete view of the service offerings of the Fraunhofer IZI will be published in April in the new Service Catalog. For individual solutions and research requests our Project Service Team as well as the research group leaders are available.

Immunological Models

- Testing biocompatibility in stem cell differentiation
- Therapy model (mice) – testing pharmaceutical agents on the human immune system

Immunotherapy – Oncology

- Imaging of biocompatibility *in vivo* (small animal) and material testing
- *Ex vivo* expanded dendritic cells – production and clinical validation
- *In vivo* bioluminescent / fluorescent imaging in small animals
- Luciferase-transgenic mice (C57 BL6, NFkB luciferase transgene)
- Clean room cell sorting (multi-parametric 11 dyes)
- Animal model mice for solid and disseminated tumors (luciferase transgene)
- Cytokine induced killer cells (CIK Cells) – production and clinical validation

Immune Tolerance

- GvHD-mice (allogene induced)
- Humanized, tripple transgenic mice
- Conditioned humanized / non-humanized mice

Vaccine Development

- Development of DNA vaccines for veterinary medicine
- Development of DNA vaccines for human medicine



Cardiorepair

- Model systems myocardial ischemia – rat/mice

Molecular Diagnostics

- Arthritis model in mice
- Cartilage destruction model in mice
- Cellular functional testing for tissue destructive fibroblasts

Neurorepair

- Experimental imaging
- Large animal model (sheep) for cerebral ischemia (Stroke)
- Histological analyses for mammal brain
- SNP analyses of the human genome
- Therapy model (rat) for cerebral ischemia (Stroke)
- Cell culture models

RNomics

- Transcriptomic analyses by tiling arrays and ultra high throughput sequencing
- Microarray analytics
- MicroRNA analytics (expression, localization, targets)
- Non-coding RNA biomarker
- Non-coding RNA biomarker for oncology, nONCOchip
- Non-coding RNA – therapy targets

Stem Cell Biology

- Cryoconservation of cells
- Reprogramming of cells – iPS (induced pluripotent stem cells)
- Stem cell analyses and stem cell manipulation

Stem Cell Technology

- Three dimensional stem cell cultures (bone/cartilage pressure training)
- Reproductive toxicology of additives and biomaterials
- Stem cell medias
- (Stem cell) cytotoxicity of additives and biomaterial
- Therapy model for tissue regeneration after fracture

Tumor Stem Cells

- Tumor stem cells (TSC) for therapy projects (production of TSC specific CD8+ CTL)
- Testing of cytostatics *in vitro* on tumor stem cells of different solid malignomas
- Testing of cytostatics and cell therapeutics *in vivo* after TSC driven tumor induction in mice model

Vascular Biology

- Defensins and anti microbial peptides
- Therapy model for arteriosclerosis/ plaque building

Virus-Host-Interaction

- Antigen specific tolerance induction
- High complexity cDNA library
- Nanometer pathogen filter
- Screening for antiviral active compounds
- Cell transduction for integrating genes in different kind of cells

Cell Engineering / GLP

- Animal model (mice) for borreliosis (*Borrelia burgdorferi*)/for diagnosis and therapy
- Animal model (mice) for salmonellosis (*Salmonella enterica*)/for diagnosis and therapy
- GLP validation for differentiated proteomic analyses (available in 2009)
- Immunotoxic GLP validation *in vitro* (available in 2009)
- Conjugation and development of antibodies
- Custom made development and validation of immunological *in vitro* test systems
- Monoclonal antibodies – development
- Polyclonal antibodies – development
- Animal model (mice) for chronic inflamed intestinal diseases/for therapy
- Validation and beta evaluation of cell technological methods and equipment

Cell Engineering / GMP

- GMP conform production of monoclonal antibodies
- GMP conform production of cell- and tissue products

Technology platform:

Antibodies

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 mainly been used for treatment of different kind of tumors and lymphomas, in treatment of rheumatoid arthritis, Crohn's disease, asthma and in 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 linking methods can be used to link signal and effector molecules.



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.

Production

Production of polyclonal and monoclonal antibodies. Optimization through molecular biological methods and/or labelling.

Development

Identification of target molecules. Development corresponding epitopes. Testing of effectiveness in laboratory scale.

Documentation

GLP conform documentation, Development of protocols and SOPs.

Process

Development of a GMP conform production process. Production of clinical test samples conform 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.

Technology platform:

Assay Adaption and Optimizing

Biotechnological and biomedical research as well as preclinical and clinical trials require valid high throughput analysing methods for detection of biomarkers, active agents and genes.

It is important to analyze samples of different origins as rapidly as possible with a high precision. Because customer demands varied 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 separate requirements of each customer. New analysis methods are then developed for and together with the partner.

The modern, high level 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 diagnostic and monitoring.

Therefore the complete value-added chain, 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 ncRNA has recently become more important as they 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.

Adaptation Analytical Platforms

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

Optimizing Parameters

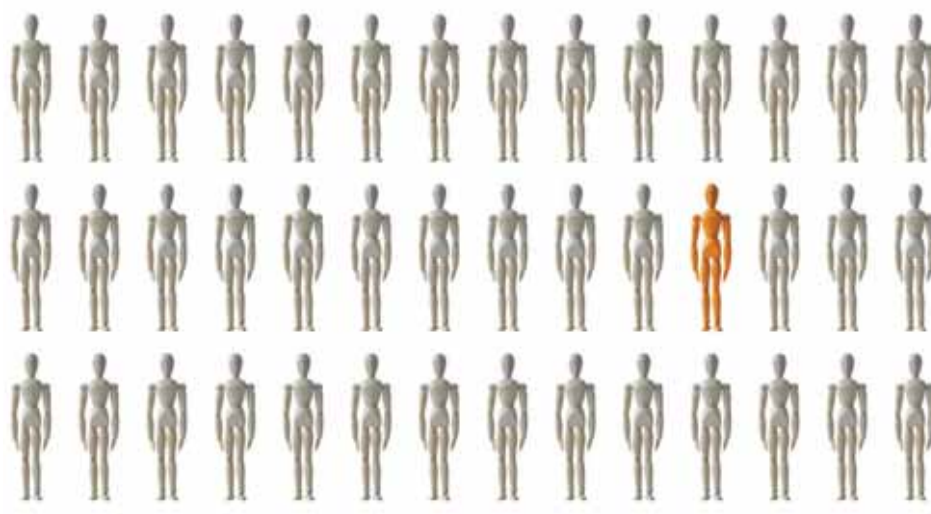
Optimization of the assay in regards to specific sensitivity, speed and costs.

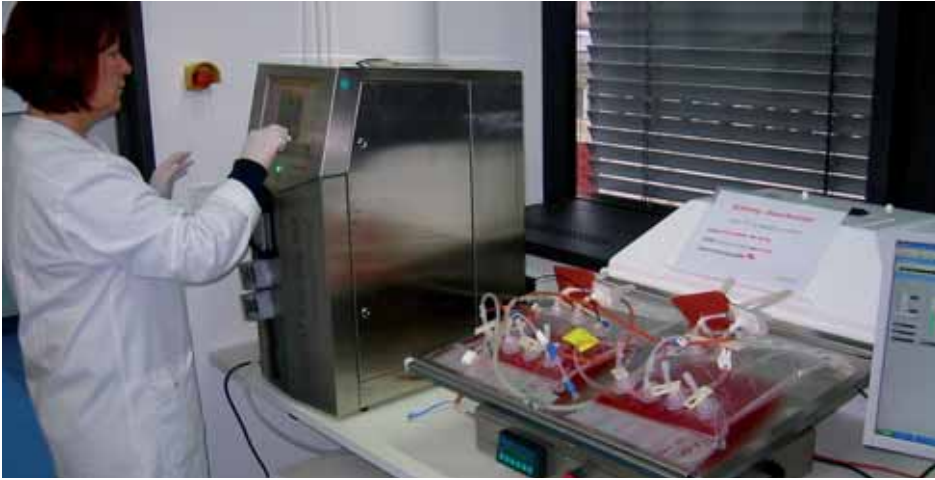
Evaluation

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.





GLP
"Good Laboratory Practice"

GMP
"Good Manufacturing Practice"

Fraunhofer IZI operates a 450 sqm GMP-compliant clean room facility.

Through the flexible design, the facility is especially attractive for new biotechnology companies that seek to bring newly developed active ingredients and 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. Most of the available clean room suites are specialized for processes associated with manufacturing of human autologous or allogeneic cell-based therapeutics (e. g. tissue engineering products, stem cell preparations, cancer vaccines). One suite is designed for the manufacturing of therapeutic recombinant proteins and antibodies in small scale (for phase I to early phase II trials).



GCP
"Good Clinical 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 Organisation for Economic Co-operation

and Development (OECD) that were devised following the EC-Directive, which were incorporated into German law and anchored in the chemical law (“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 possesses a separate GLP laboratory and trained personnel. These resources are fully equipped to provide integrated research and development solutions.

In addition to the clean rooms and the technical and, respectively, regulatory 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 Pharmaceutical Act (AMG).



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 institutional 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 focus here is primarily on trials with walk-in patients. 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.

Career Development Offers

The Fraunhofer IZI places significant value on the training and career development of its employees and co-workers. The private academy WSR has been working successfully together with the Fraunhofer IZI over the last four years. The seminar rooms and the modern ambience in the new central building of the institute offer ideal conditions for this unique cooperation.

The services of WSR cover the entire career development training spectrum with emphasis on internal and external communication. The various career development offerings are supplemented scientifically with cutting-edge seminars held by top Fraunhofer researchers.

Both Fraunhofer IZI and WSR work with selected trainers and coaches, who all possess a university education and several years of practical knowledge. Thus they all have the necessary experience and authority, and above all the proper temperament in regards to educational and psychological classroom goals.

Commitment, motivation and responsibility are for each employee and co-worker the most important success factors and essence of personal achievement. The Fraunhofer IZI is delighted to support external knowledge seekers as well. All of the following seminars can be offered as in-house seminar if arranged in advance.



More information concerning seminars can be found in our seminar catalog or by contacting:

Christina Kühn
Phone: +49 (0) 341 / 355 36-9322
Fax: +49 (0) 341 / 355 36-8 9300
christina.kuehn@izi.fraunhofer.de

www.izi.fraunhofer.de



Interdisciplinary Seminars

Communication

- communication training
- good form in telephone – contacts as business card
- communication for assistants of management/executive board
- customer-oriented correspondence

Business Administration

- business administration basics
- successful procurement of third-party funding
- business start-up (basics)

Law

- employment law
- business law
- company law
- assertion and enforcement of receivables
- contract law (basics)
- scientific patent law
- collective agreement for the public sector (employees)

Human Resource Management

- management seminar I
- management seminar II
- conference management and moderation
- team work
- conflict training
- contemporary personnel work

Methodology

- basics of marketing
- project management (basics)
- project management (advanced)
- successful negotiation
- sales training
- presentation training
- creativity training

Self and Time Management

- how to handle your time
- stress reduction / stress management

Scientific Seminars

- scientific writing
- good clinical practice for investigators
- immune fluorescence microscopic applications
- radioactive labeling for molecular biological and cell biological applications



Groups and Selected Projects



Cell Engineering / GMP Group

Contact

Dr. Gerno Schmiedeknecht
Phone: +49 (0) 341/355 36-9705
gerno.schmiedeknecht@izi.fraunhofer.de

Competencies

- pharmaceutical clean room facility for aseptic manufacturing of investigational medicinal products with references
- quality control laboratory with qualified analytical devices
- comprehensive experience in process development
- highly qualified personnel for manufacturing, quality control and quality management

A range of products and services of this group can be found on page 28-29.

Profile

This group maintains modern clean room facilities for the manufacturing of investigational medicinal products according to Good Manufacturing Practice (GMP). Our expertise is primarily in the areas of cell-based therapeutics (e. g., tissue engineering products), therapeutic recombinant glycoproteins and antibodies. Our services span all phases from process development to the manufacturing of investigational medicinal products.

Project: Manufacturing of Stem Cell Therapeutics for Stroke

Background

One of our most advanced current projects in the field of regenerative medicine is the establishment of a GMP-compliant manufacturing process for autologous cell therapy for the treatment of ischaemic stroke. This novel therapeutic approach, in which stem-cell containing populations from the patients own bone marrow will be intravenously applied during the acute phase of stroke, has been developed over the last few years at the Fraunhofer IZI by the institute's Neurorepair

Group and has already been successfully pre-clinically tested in small and large animals (rat, sheep) in regard to efficacy and safety. Ischaemic stroke is in addition to cardiovascular diseases, cancer and diabetes one of the main causes of death in the Western World. According to current surveys, there are about 165,000 cases of stroke in Germany every year. Following an acute stroke some 40 percent of patients die within the first year while another 35 percent are in need of constant attention. In order to guarantee a sufficient supply of



View of the GMP facility of the Fraunhofer IZI.



The Cell Engineering/GMP Group.

these stem cell containing preparations for future clinical trials, the Cell Engineering GMP Group of the Fraunhofer IZI intends to apply for a manufacturing authorisation according to §13 German Pharmaceuticals Act (AMG) for investigational medicinal products once the GMP processes have been developed and the manufacturing steps and quality controls are established.

Aims

The main goal of the project is to ensure the future safe and reproducible manufacturing of investigational medicinal products for an initial pilot clinical trial for the treatment of acute ischemic stroke in humans. The official confirmation for a safe and reproducible manufacturing process is the approval of a manufacturing authorisation according to §13 German Drug Act by the responsible pharmaceutical authorities of the Free State of Saxony in coordination with the higher Federal authority, the Paul-Ehrlich-Institute. One of the preconditions for the granting of such a manufacturing authorisation is, among others, the qualification of the

clinical organisation involved in the procurement of the patients bone marrow. This requires a procurement authorisation according to § 20b German Pharmaceutical Act. Fraunhofer IZI's modern GMP clean room facility, with its design, equipment and staffing specifically specialised for the production and quality control of such novel cell-based medicinal products, represents a suitable technological environment for a rapid and high-quality, practical realisation of the goals mentioned above.

Results

A number of milestones on the road to a manufacturing authorisation have already been achieved. Following the presentation of the process design to the pharmaceutical authorities, great importance was attached to improving the standard isolation protocol (density centrifugation using Ficoll 1.077) for the stem-cell enriched mononuclear cell fraction from bone marrow. Through the use of unpublished methods for the separation of human bone marrow it was possible to improve the yield of mononuclear cells up to tenfold and to minimise the loss of stem cells to a minimum. Another essential task was the GMP-compliant generation of a manufacturing formula, standard operating procedures (SOPs) for all processing and packaging steps including protocols for documentation, a specification for the final investigational medicinal product, SOPs for all quality control methods including protocols for documentation, specifications for starting materials as well as SOPs for stability testing of these starting materials. The process development



The Flow Cytometry and Quality Control laboratory.



The clean room class B for the production of cell therapeutics.

involved the production of first test batches in IZI's clean rooms, chiefly in order to establish the manufacturing steps and the necessary quality controls and for training of the involved staff. In addition, detailed validation plans were scheduled in order to prepare the process validation according to Annex 15 of the EC-GMP-Guideline and the validation of the quality control methods according to ICH Guideline Q2A/Q2B and to the European Pharmacopoeia.

Potential

The next step is the manufacture of the necessary three validation batches according to Annex 15 EC-GMP-Guidelines and the preparation of the accompanied validation reports. Furthermore it will be of importance to implement all requirements for obtaining permission for the procurement of bone marrow according to the standards of the § 20b German Pharmaceutical Act / EC Guideline 2006/17/EC within the anticipated clinical trial centre. Afterwards the application for a manufacturing authorisation according to § 13 German Drug Act will be filed. After granting of the manufacturing authorisation by the responsible pharmaceutical authorities of the Free State of Saxony, initial investigational medicinal products can be manufactured and provided to the clinical trial centre. As a result of this internal development project, the Cell Engineering GMP team at IZI has gained the experience

to become qualified as a competent partner for the GMP-compliant implementation of various cell therapy projects in a variety of areas in addition to field of bone marrow derived stem cell therapies. Given the rapid development of regenerative medicine and stem cell research, projects of this type are expected to increase exponentially in the next few years.



Visual control of cell cultures in the clean room class B.



Work in the clean room.

Special Background

The EC-GMP Guidelines for Medicinal Products for Human and Veterinary Use and its annexes describe the basis for GMP production of cell-based medicinal products. Annex 1, "Manufacture of Sterile Medicinal Products," is of particular relevance to this project due to requirements for aseptic production. Furthermore, the European Guidelines, 2004/23/EC, 2006/17/EC and 2006/86/EC, provide an extensive overview of the particular requirements of this product group. The European Parliament's Regulation No. 1394/2007 on advanced therapy medicinal products that modifies the Directive 2001/83/EC and Regulation No. 726/2004, is quite significant. This regulation will lead to a far-reaching harmonization with regard to the production, testing and approval of cell therapeutic products. In addition

to the European requirements, one must also adhere to the national legislation, for example, the German Pharmaceutical Act (AMG), the German Ordinance for the Production of Medicinal Products and Active Substances (AMWHV) and the Legislation regarding the Quality and Safety of Human Tissue and Cells (Gewebegesetz).



Cell Engineering / GLP Group

Contact

Dr. Jörg Lehmann
Phone: +49 (0) 341/355 36-1205
joerg.lehmann@izi.fraunhofer.de

Competencies

- Antibody production (monoclonal or polyclonal)
- Proteomics
- Immunotoxicology
- *in vitro* assay development (e.g. ELISA)
- Animal models (mouse: infections, chronic-inflammatory intestinal diseases; dog (Beagle): blood product testing – GLP)

- Flow cytometry
- Immunofluorescence, immunocytochemistry
- Cell sorting (MoFlo, MACS, Dynabeads)

A range of products and services of this group can be found on page 28-29.

Profile

This group has established a GLP laboratory for conducting immunotoxicological GLP studies (*in vitro*) as well as differential proteome analyses. The second focus is the identification and validation of novel biomarkers to be used in the diagnosis or the therapy of chronic-inflammatory or tumor diseases through the use of immunological, cell-biological and protein-biochemical approaches.

Project: Differential Proteom Analysis of UVC-treated Versus Untreated Canine Platelet Concentrates

Background

Pathogen inactivation of thrombocyte preparations through UVC radiation is a promising method to minimize contamination with bacteria and viruses. But it remains unclear as to which extent the UVC radiation alters the quality of the thrombocytes or in this case, causes unwanted or harmful effects in the patient receiving the cells. It has been shown that UVC radiation induces oxidative damage to proteins through generation of reactive oxygen species.

Furthermore, photolysis of disulfide bridges also occurs which causes a modification of the cysteinyl-thiol group of a subset of thrombocyte and plasma proteins. Such protein modifications may have the potential to cause an immune reaction in the host. In this context the modified proteins are called "neoantigens". The immunization of the recipient against UVC-induced neoantigens might have serious consequences for the transfused patient (i.e. generation of thrombocyte-specific an-



Work in the hybridoma laboratory.



Cell Engineering / GLP Group in front of the new Fraunhofer IZI building.

tibodies or thrombocyte-reactive T-cells) which may lead to a refractory status or a thrombocytopenia. A further potential risk consists in the fact that thrombocytes themselves are part of the immune system. Due to the fact that they release cytokines and chemokines (e.g. TGF- β , PAF, soluble CD40 ligand, RANTES), thrombocytes are capable of mediating immunomodulatory effects.

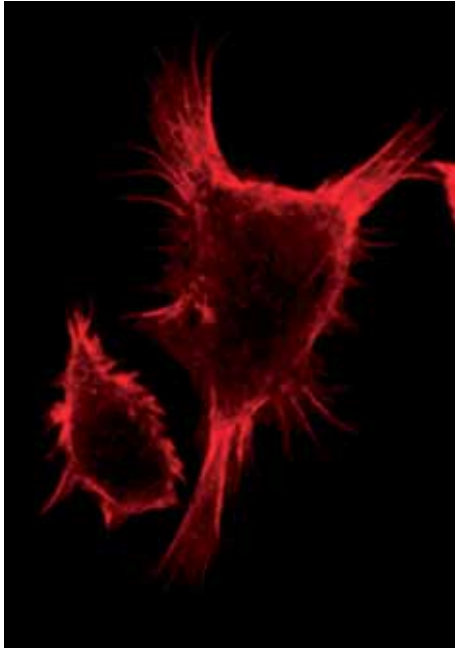
Aims

In order to identify possible adverse effects of UVC radiation on the platelet or plasma proteome which would result in the formation of neo-antigens, an immunization experiment with UVC-treated and untreated (control) platelet concentrates was performed in dogs (beagles) in cooperation with and as a research and development service for the Blood Donation Service of the State Group of the DRK (Blutspendedienst der Landesverbände des DRK) Niedersachsen, Sachsen-Anhalt, Thüringen, Oldenburg und Bremen gGmbH Springe. UVC-induced modifications of thrombocyte and plasma proteins and thrombocyte lysates derived from UVC-treated and untreated platelet concentrates were analyzed through two-dimension high-resolution plasma gel electrophoresis. Immunogenicity was investigated by western blotting using immune sera from treated dogs.

On the basis of the obtained data we will ascertain the potential immunotoxicological risk of the routine application of UVC treatment of platelet concentrates.

Results

Up to the end of the research period 2008, no significant protein modifications were detectable following UVC treatment. Currently, western blot analyses are in progress in order to test the sera of the dogs for platelet-directed auto-antibodies which are potentially induced through UVC treatment.



Immunofluorescence: staining of cytoskeleton of myeloid progenitor cell line MuSC-E8 by Phalloidin-TRITC.



Dr. Jens Knauer carrying out flow cytometric analysis of cells.

Potential

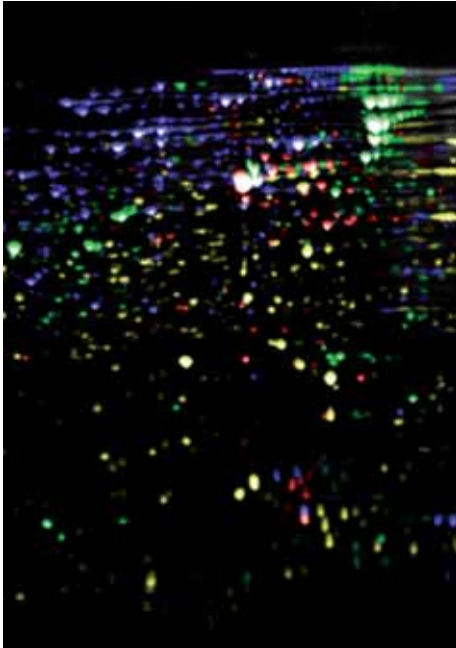
If this pre-clinical study in the beagle model does not result in significant adverse effects to the plasma and/or the thrombocyte proteome, the next step would be to start a phase I clinical trial.

Further Projects

A significant emphasis of our work in the years 2007 and 2008 was the establishment of several mouse models. Among these are disease models for investigation of immunity to infection (i.e. Salmonella, Borrelia), chronic-inflammatory bowel diseases (i.e. DSS colitis, TNBS colitis), and Sepsis/SIRS. Meanwhile, our group is preparing to use these disease models for testing experimental therapy approaches (e.g. nanoparticle-encapsulated kinase inhibitors) or alternatively will use them to test exogenic immunomodulatory noxes (e.g. heavy metals).

The applicability of these animal models for use in industry-supported research and development studies has been notably demonstrated within a relatively short time. For example, the Salmonella infection model was used for preclinical testing of a novel, innovative method for the early diagnosis of emerging infection diseases as a research service

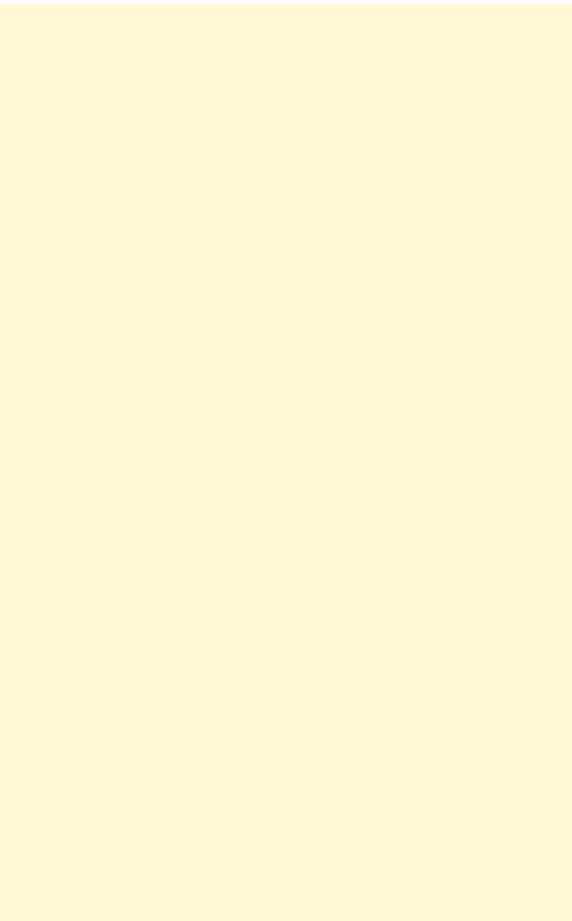
contract for the Norwegian biotech company PlasmAcute AS. The Borrelia infection model has been used for the evaluation of a novel local bactericide treatment following tick bites as a service contract for IXODES GmbH Zürich. Moreover, the DSS colitis model is currently being used to evaluate a novel therapy approach for treatment of celiac disease for the biotech company ZEDIRA GmbH Darmstadt. The successful application of our mouse models in these industry settings demonstrates their versatility and value in regards to saving time and cutting costs in pre-clinical and diagnostic research and development.



Differentiated proteome analysis by DIGE-technology.



GLP-conform production of monoclonal antibodies at laboratory scale with a 20L-WAVE-Bioreactor.





Immunological Models Group

Contact

Dr. Manja Kamprad
Phone: +49 (0) 341/97 25-830
manja.kamprad@izi.fraunhofer.de

Competencies

- *in vitro/in vivo* characterization of hematopoietic stem cells
- *in vitro/in vivo* characterization of mesenchymal stem cells including immunomodulatory properties
- human hematopoietic recovery in mice
- risk analysis of biological compounds and materials on hematopoietic and mesenchymal stem cells
- risk analysis of biological com-

pounds and materials on erythrocytes, thrombocytes, lymphocytes, phagocytes

A range of products and services of this group can be found on page 28-29.

Profile

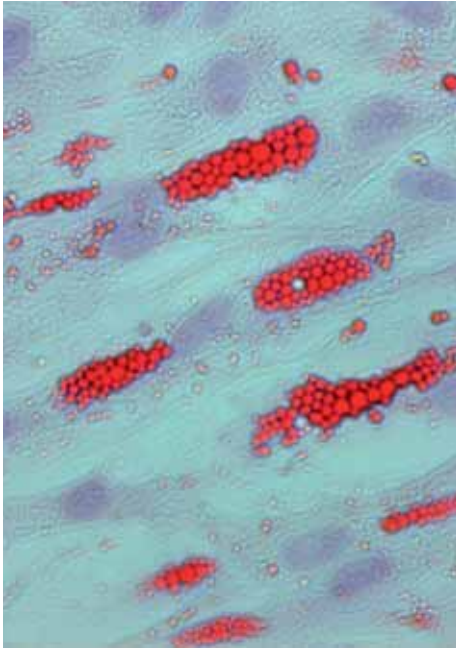
This group is focused on the isolation, cultivation and the phenotypical and functional characterization of mesenchymal and hematopoietic stem cells for the development of regenerative therapies. Based on the formation of functional human immunocompetent cells in a mouse model, the development of disease models and therapy processes are being pursued in cooperation with the University of Leipzig.

Project: New Tissue Sources of Stem Cells

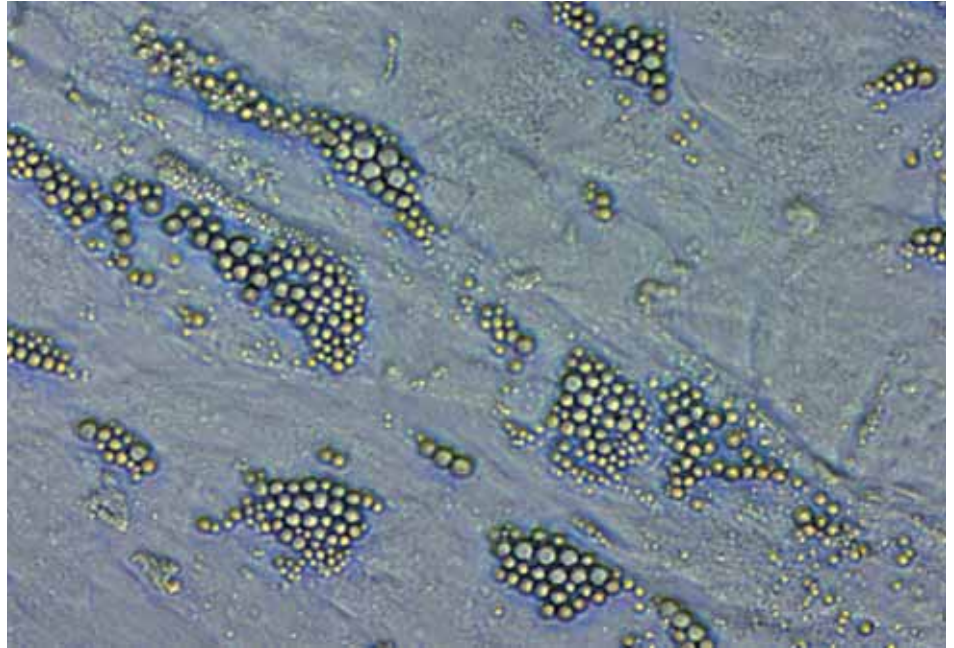
Background

Cell-based regenerative therapies are based on promising functional plasticity of stem cells. Traditional sources of stem cells for regenerative therapies such as bone marrow, peripheral blood, and umbilical-cord blood contain a low amount of haematopoietic and mesenchymal stem cells. The isolation of cells from bone marrow and peripheral blood entails considerable invasive

surgical techniques. Cord blood can only be obtained once and the cell yield is often insufficient for therapeutic purposes.



Adipocytes with red stained fat enclosures; the cell nucleus is shown in blue.



Phase contrast image of unstained cells during the development of fat from mesenchymal cells.

Aims

Therefore, there is a need to examine other sources of tissue to find out whether tissue-specific primary cells exhibit stem cell characteristics irrespective of their differentiation state.

Results

Two sources of cells not previously used for regenerative therapies were extensively examined in terms of their mesenchymal stem cell potential. It was shown that isolation and expansion of primary cells from tissue without invasive procedures take place irrespective of the age of the donor. Short-term as well as long-term expanded cells demonstrated a phenotype that is comparable with mesenchymal stem cells. Using *in vitro* differentiation techniques, a pronounced chondrogenic stem cell potential was detected in all donor cultures. However, under *in vitro* conditions, the cells were not able to differentiate into bone and fat cells.

Potential

The results demonstrate that apart from traditional stem cell sources, other cell resources are also available, which possess cells with typical mesenchymal characteristics. Since cells can be obtained using non-invasive methods, these sources can be used more than once; this is of immense therapeutic interest. The possibility to isolate potentially regenerative cells into old age is especially significant for autologous regenerative treatment strategies.



Vaccine Development Group

Contact

Dr. Sebastian Ulbert (Head of Laboratory)
Phone: +49 (0) 341/355 36-2106
sebastian.ulbert@izi.fraunhofer.de

PD Dr. Matthias Giese (Head of Group)
matthias.giese@izi.fraunhofer.de

Competencies

- platform technology for the development and validation of DNA vaccines for application in veterinary medicine (prophylactic and, species-dependent, also therapeutic)
- potential for the development of similar DNA vaccines for human medicine
- zoonosis research
- parasite research

A range of products and services of this group can be found on page 28-29.

Profile

This group is developing marker vaccines for use in veterinary medicine. Primary activities include research on DNA vaccines, but also vector and sub-unit vaccines against viral infections in pigs, horses and in pets. Additionally, in January 2007, an extensive project on West Nile virus began, fully supported by the BMELV. The development of a human vaccine against this zoonotic virus is planned.

Project: West Nile Virus: Development of a Vaccine and a Diagnostic Test

Background

West Nile virus (WNV), first isolated in 1937 in Uganda's West Nile District, is a zoonotic neuropathogen which can cause encephalitis. This virus infects not only birds, horses and many other mammals but also humans. WNV is transmitted by mosquitoes. Birds evidently constitute the natural reservoir of WNV; mosquitoes then acquire the virus from infected birds when feeding on their blood. WNV is spread from endemic areas partly by birds migrat-

ing between Africa, Asia and Europe. WNV first broke out in the USA in 1999 and within a span of 5 years infected the entire North American continent. Numerous humans and animals were infected and a portion of the victims died. Following a drastic increase in the number of fatal WNV infections among humans in 2002 and 2003 in the USA (9,862 cases of the disease were recorded in 2003, of which 264 proved fatal), the number of people affected declined in 2004 and 2005.

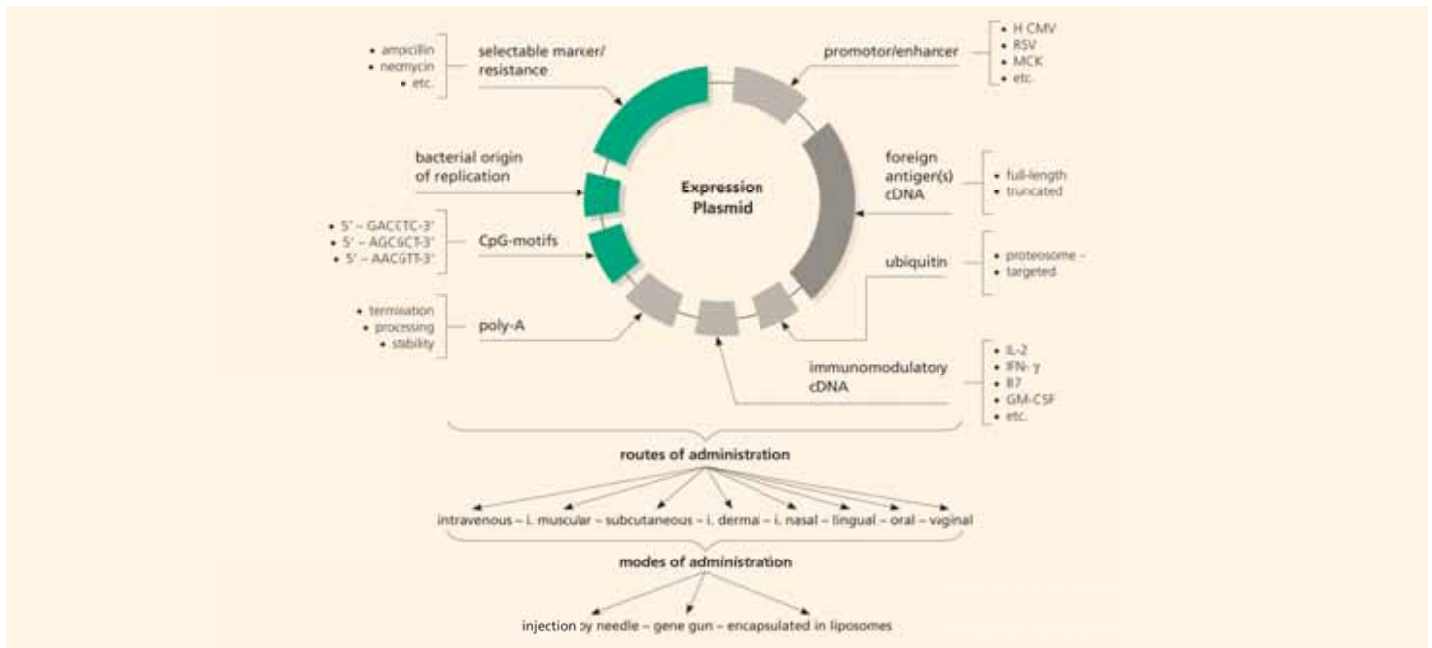


Diagram of an expression plasmid for DNA vaccination. The antigen is under the control of promoters/enhancers and the poly(A) sequence. The co-expression of various cytokines and ubiquitin contributes to immunomodulation. CpG motifs support the unspecific immune reaction and are part of the plasmid's bacterial backbone.

In contrast to the USA, almost nothing is known about the spread of WNV in Europe. Over the past few years, the virus has been detected in a number of European countries. According to a recent study, WNV has already reached the UK, probably being spread there by birds. In France, WNV has been observed since the year 2000, and was first detected in the Pyrénées-Orientales in 2006. However, no studies have been carried out into the prevalence of WNV in Germany. Moreover, so far no human vaccines against WNV have been developed anywhere in the world. As far as veterinary medicine is concerned, just one vaccine has been licensed for horses in North America, but there are no vaccines that can treat different species.

Aims

The objective of the project/program is to study the spread of WNV in Germany and to develop a vaccine that can be used on different species all over the world. A three-pronged approach has been adopted, comprising epidemiological studies on wild birds and horses, the establishment of a mouse infection model with diagnostic marker, and the development of a DNA vaccine, which will initially be tested on horses.

Results

Over the last few years, a DNA vaccine has successfully been developed against a viral infection in horses (EAV/equine arteritis virus). This vaccine is not only being used in clinical studies prophylactically, but also for therapy of EAV-infected horses.

Potential

DNA vaccines are also referred to as third-generation vaccines. They are modern, highly efficient and biologically safe vaccines, which furthermore can also be produced inexpensively. GMP-conform production is possible at Fraunhofer IZI. First DNA vaccines are already registered for animals and in preparation for humans.

Special Background

DNA vaccination refers to the application of pure plasmid DNA in a eukaryotic expression vector in order to activate a complete immune response. This plasmid DNA bearing an antigen of the pathogen is usually applied intramuscularly, subcutaneously or intravenously, although oral administration is also effective.



Immune Tolerance Group

Contact

Dr. Stephan Fricke
 Phone: +49 (0) 341/355 36-2205
 stephan.fricke@izi.fraunhofer.de

Competencies

- experimental therapy models for xenogenic and allogeneic GvHD
- experimental cell culture models for testing of therapeutically relevant monoclonal antibodies
- chemotherapy in animals
- histology / immunohistology
- cell transplantation procedure in rodents

- production and analysis of histology slides (animal models)
- production of regulatory T cells
- ELISPOT assay
- automatic and quantitative fluorescence microscopy

A range of products and services of this group can be found on page 28-29.

Profile

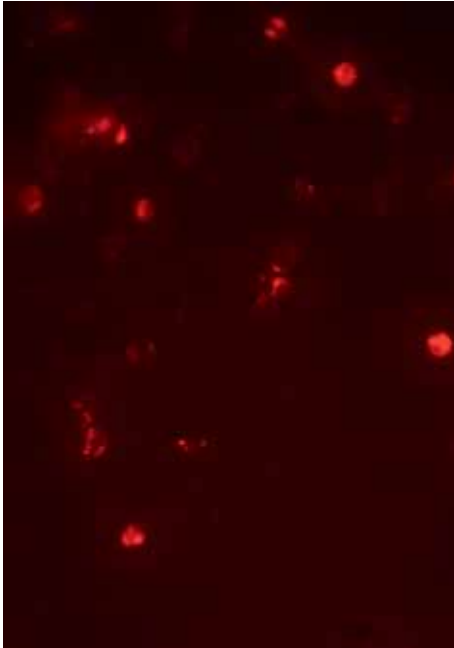
The goal of this group is the development of cell- and antibody-based therapeutic strategies to treat complications following hematopoietic stem cell transplantation. Novel concepts of immunological tolerance oriented towards immunologic and therapy associated complications (e. g. GVHD) are being tested in new, in-house developed animal models.

Project: Alleviating Complications of Hematopoietic Stem Cell Transplantation

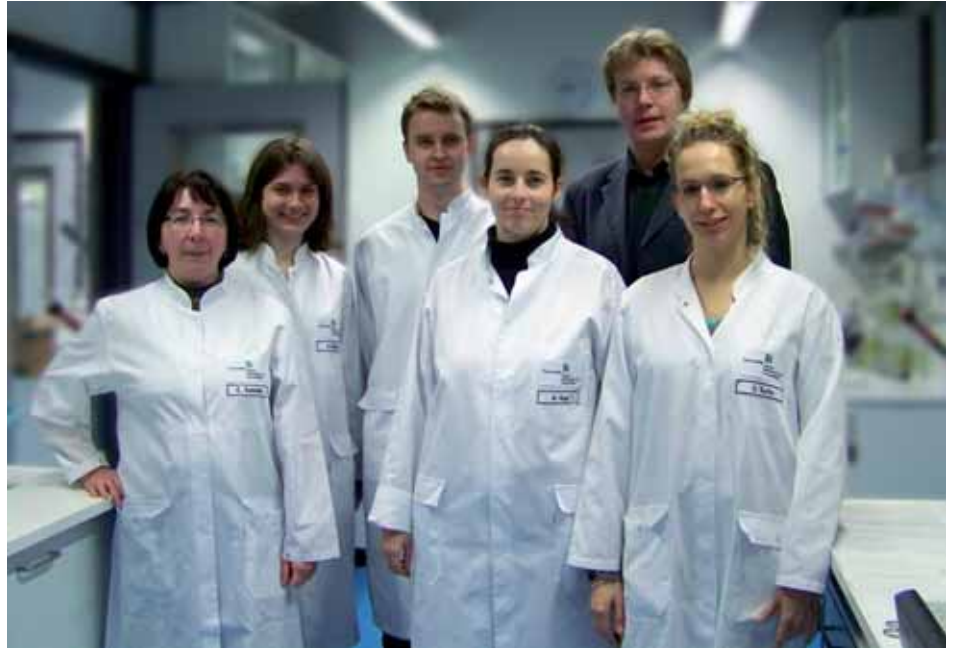
Background

Hematopoietic stem cell transplantations (world wide over 60,000 per year) are the only curative treatment option for many hematology-oncology patients. Despite remarkable successes with this therapy, patients are susceptible to many treatment-associated complications, in addition to the primary disease. Particularly infections, due to the organ toxicity of chemotherapy, radiation or supportive therapy, as well as Graft versus Host Disease (GvHD), lead to significant problems. Acute

GvHD occurs in up to 78 percent of patients, chronically in 64 percent of the incidences. In order to efficiently reduce the incidence of GvHD, stem cells must be transplanted that can renew the hematologic system and support a rapid reconstitution of immunological competence. Current therapies (immunosuppressives) often need to be taken over a lifetime, have many side effects and are only successful in a limited sense. Treating such complications cause significant costs (over 140,000 euros per patient).



Phenotype of peripheral blood cells of triple-transgenic mice. Detection of the human MHC-II (HLA-DR3)-molecule by immunofluorescence microscopy.



Immune Tolerance Group.

Aims

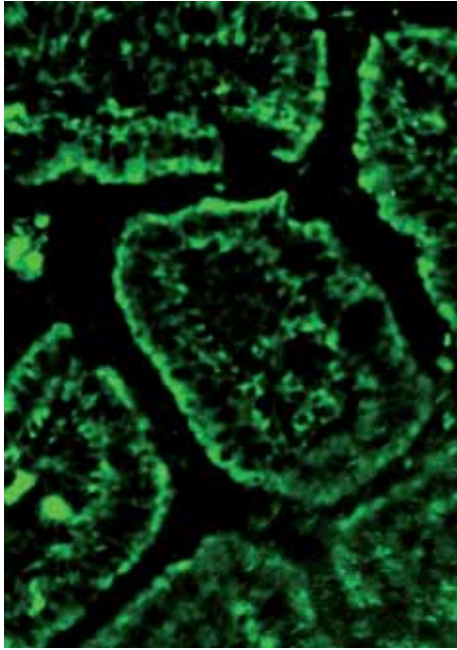
There is a pressing need for new therapies that will minimize complications following stem cell transplantations. The effectiveness of such new therapies must be measured by the reduction or prevention of the associated complications. Using a human CD4+, murine CD4-, human DR+ transgenic mouse line used by this group, transplantation models are being created for the pre-clinical testing of therapies. The triple-transgenic mouse expresses a human CD4 and MHC-II molecule while, at the same time, the murine CD4 molecule is not expressed. This makes it possible to simulate the interaction of human molecules in an animal model and to influence them therapeutically. Cell therapy strategies and induction treatments with anti-T-cell antibodies should lead to clinically applicable treatments.

Results

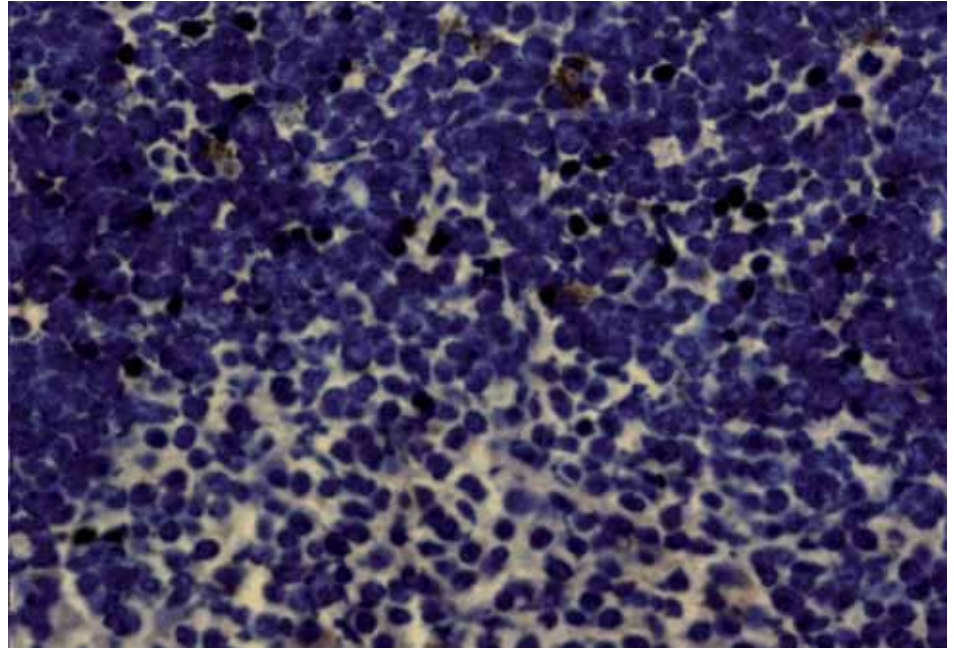
Through the confirmation of the results of 2007, the following new results could be attained (*in vivo* and *in vitro*):

- 1.) The comparison of transplantation of hematopoietic stem cells (HSC), mesenchymal stem cells (MSC) and bone marrow cells (BMC)
- 2.) Establishment of a chronic GvHD model (C57Bl/6 [H-2b] in C57Bl/6 x BALB/c [H-2b x d]) in wild type-mice
- 3.) Establishment of an objective analysis method for the diagnosis of GvHD by full automated and quantitative fluorescence microscopy
- 4.) Enlargement of PCR assays, FACS assays and immunohistology regarding specific marker for sub-classification, quantification and analyses of chimeric transplanted cells (human/mice) which had been transplanted into different organs of the recipient

- 5.) Production of therapeutic and chimeric anti CD4 antibodies from hybridoma cells and proof of effectiveness in triple transgenic mice
- 6.) Confirmation of concentration dependent therapeutic effects of anti-CD4 therapy in triple transgenic mice (*in vivo* and *in vitro*)
- 7.) Expansion of regulatory T-lymphocytes
- 8.) Confirmation of concentration dependent, suppressing effects of regulatory T-lymphocytes (CD4+, CD25+, FoxP3+) *in vitro*
- 9.) Flow-cytometry-based characterization of mesenchymal progenitors and description of their engraftment conditions after stem cell transplantation



Automated fluorescence microscopy of the small intestine of C57Bl/6 wildtype-mice; direct immunofluorescence with AlexaFluor405 linked anti-CD8 antibodies.

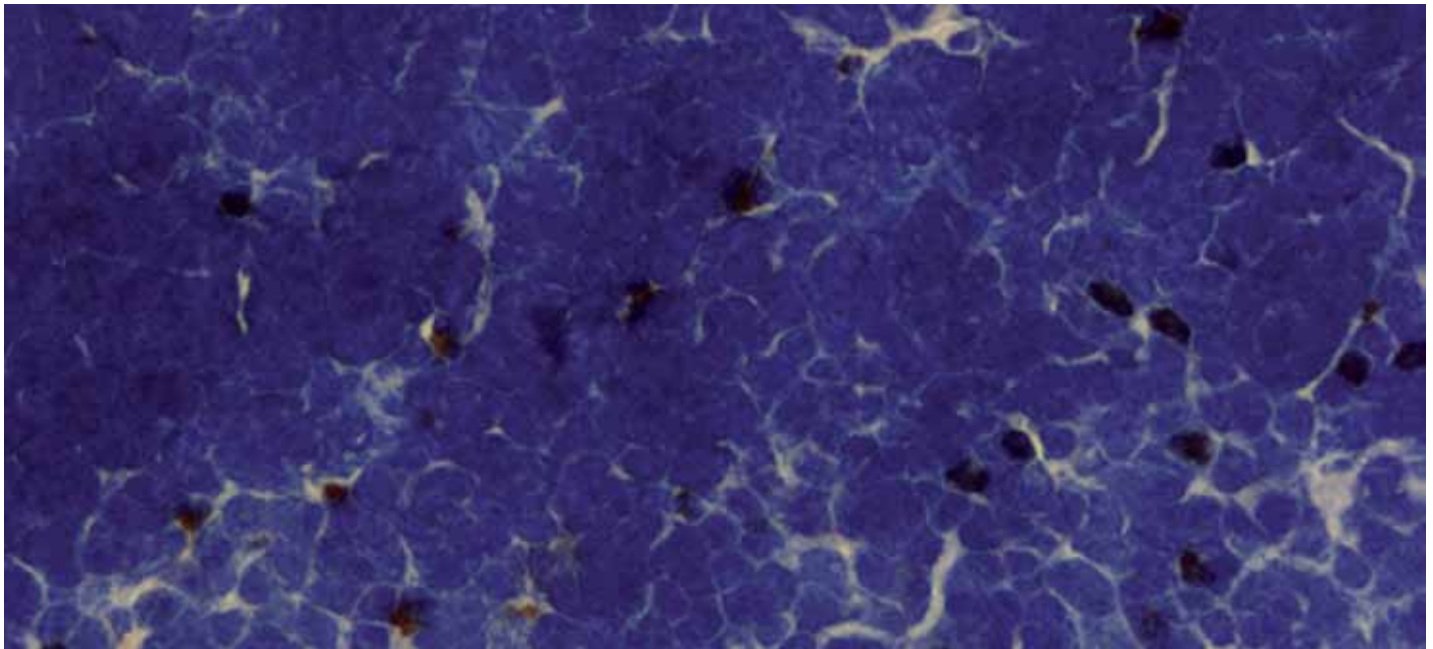


Immuno-histological image of regulatory T-lymphocytes in milt tissue of C57Bl/6 wildtype-mice.

Potential

In the past decades, increasingly sophisticated therapeutic strategies have been developed in hematology / oncology. The optimized therapies, however, have resulted in increased therapy associated short-, middle- and long-term complications. To control these complications, optimal techniques and applications still need to be developed, in order to improve the chances of recovery of the patient. Testing new therapies requires developing suitable *in vitro* and *in vivo* models, in order to bring promising treatments more rapidly into clinical application. The presented results show that in a transgenic mouse model, the transplantation of various murine and human cell fractions is possible and that their therapeutic effect can be more precisely characterized in a model

system. The anti-CD4-antibody applied in these studies could be utilized as a therapeutic option in hematologic stem cell transplantations to control T-lymphocytes. Results derived from this transplantation model could furthermore be used for other immunology and oncology based disease patterns that involve GvHD reactions.



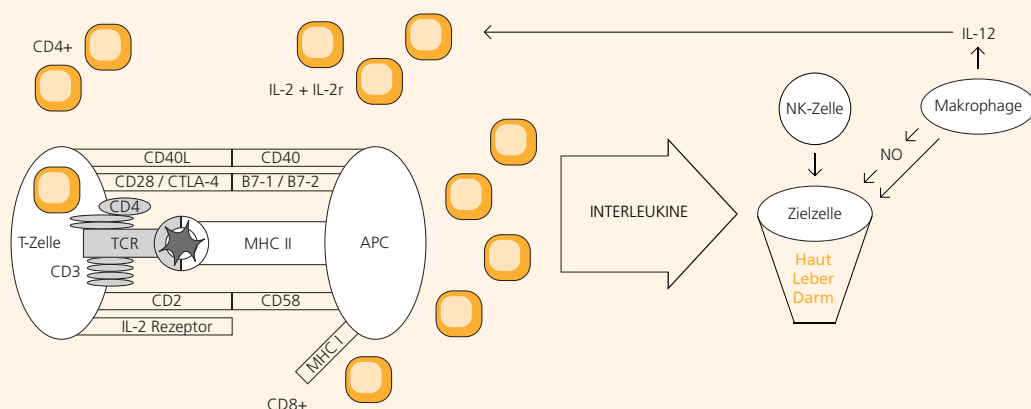
Immunohistological image of regulatory T-lymphocytes in Thymi of C57Bl/6 wildtype-mice.

Special Background: Graft versus Host Disease

Graft versus Host Disease (GvHD) is the main complication following hematopoietic stem cell transplantations. T-lymphocytes contained in the donors graft react against the recipient's tissue and identify the recipient's tissue as foreign. The process is comprised of multiple pathophysiologic levels. Through chemotherapy and radiation, which is a necessary step in the treatment prior to stem cell transplantation,

proinflammatory cytokines are released and antigen-presenting cells (APCs) are activated in recipient tissue. These molecules and cells activate the T-cells contained in the graft, which, as a result, release cytokines that recruit cytotoxic T-lymphocytes, monocytes, macrophages and natural killer cells. Because of these effector cells and the continuous cytokine release, pathophysiological processes are reciprocally

stimulated through a positive feedback loop which strengthens the GvHD. This establishes a systemic disease profile with specific effects on skin, liver, intestine and eyes. A moderate form of GvHD can however be of benefit to the patient, because the T-lymphocytes of the graft can also destroy remaining tumor cells in the host (Graft versus Leukemia Effect).





Virus-Host-Interaction Group

Contact

Dr. Jörg Baumann
 Phone: +49(0)341/355 36-2505
 joerg.baumann@izi.fraunhofer.de

Dr. Sabine Breun
 Phone: +49(0)341/355 36-2506
 sabine.breun@izi.fraunhofer.de

Competencies

- molecular mechanisms of retroviral infections, in vitro analysis of antiviral vaccines and active agents
- various cell culture systems for the examination of viral infections and their prevention, mucosal HIV transmission system
- mutational analyses, molecularbiological, cell-biological, immunological and biochemical studies
- analysis of endogenous retrovirus activation
- real-time-PCR quantification of intracellular retroviral products

- in vitro differentiation of hematopoietic cells
- modulation of immune cells
- flow cytometry, incl. the possibility of sorting under BL-2 conditions
- viral and non-viral transduction of various cell systems
- experiments possible under BL-3 conditions

A range of products and services of this group can be found on page 28-29.

Profile

The group studies the many aspects of the interaction of the virus with its host. The main focus is the development of new antiviral prevention and treatment strategies. To this end, we study the as yet poorly understood mechanisms of innate intracellular defence against viral infections and the influence of co-factors of the host cell. Furthermore, we aim to achieve a modulation of the immune response.

Project: Development of New Antiviral Strategies and Tools

Background

Worldwide about 33 million people are infected with HIV; today about 1 percent of the adult population carries the virus, of these 2 million are children under age of 15. In 2007 alone, 370000 people were infected with HIV. Every year, 2.7 million die of the acquired immunodeficiency syndrome (AIDS), meanwhile more than 20 million people died as a direct cause

of AIDS (UNAIDS Report 2008). Two dozen drugs are currently approved that are able to suppress the virus for a number of years. However, it is just a matter of time until the virus population escalates due to the high mutation rate of the virus. Instead of attacking the virus itself, the Virus-Host-Interaction Laboratory identifies new targets in the cell that are essential for the virus life cycle. The virus propagation

vector development	nanotechnology and biomedicine	virus-host-interaction	immune modulation	Service and contract research
development and modification of expression systems	development of diagnostic, monitoring and therapeutic approaches <i>in vivo</i>	new approaches for therapy and antiviral strategies	directed manipulation of immunological reactions	related to the platforms (left): 1) analyses of molecular mechanisms 2) testing of potential antiviral agents 3) cell culturing systems 4) screening systems 5) production of cell lines and cell populations 6) transfection, transfection kit 7) infection of cells 8) production of retroviruses and retroviral vectors 9) production of complex cDNA libraries from different kinds of cells and tissues 10) state-of-the-art techniques in molecular biology, immunology, virology, cell biology and biochemistry 11) consulting
1) for different kinds of cell types (e.g. stem cells, neuronal cells) 2) for certain kinds of tissue 3) with certain characteristics 4) for targeted applications	nano materials in combination with 1) pathogens 2) cells (cell culture) 3) tissue 3) or as carrier	1) prevention 2) discovering new intracellular targets for following therapies	directed manipulation of: 1) T-cell response 2) immune cells	
interesting for:				
basic research applied research	basic research applied research	basic research	basic research applied research	cooperations contract research
academic partners industrial partners	academic partners industrial partners	academic partners industrial partners	academic partners industrial partners	academic partners industrial partners

Virus-Host-Interaction: platforms.

may be stopped or inhibited; the virus will not be able to circumvent the block through a single mutation. In addition, research carried out in the lab will improve the knowledge of the immune response and its mechanisms of regulation, which will be used for specific modulation of the immune system. Through the use of HIV, retroviral vectors, immune cells and nanotechnology, the laboratory has developed further platform technologies, that are used for the development of antiviral strategies, a specific modulation of immunological reactions, the development of new diagnostic tools, and the development of disease models.

Aims

The Virus-Host-Interaction Laboratory was founded in 2006 at the Fraunhofer IZI. Dr. Joerg Baumann and Dr. Sabine Breun established the group on the basis of results and concepts developed over a five year period at the National Cancer Institute, HIV Drug Resistance Program, USA. Research cooperation with groups in Germany, other European countries and in the USA and Africa, have enabled the laboratory to develop new strategies to fight HIV/AIDS and other pathogens – starting with basic research which leads to applied research in the future. In the area of applied research the team has developed platforms that offer specific benefits for partners that are interested in cooperation and/or contract research in the areas of HIV research and nanotechnology/biomedical research:

Virus-Host-Interaction

Isolation and characterization of unknown co-factors and resistance factors; Investigation of the role C-type lectins play in HIV pathogenesis and other diseases.

Vector Development

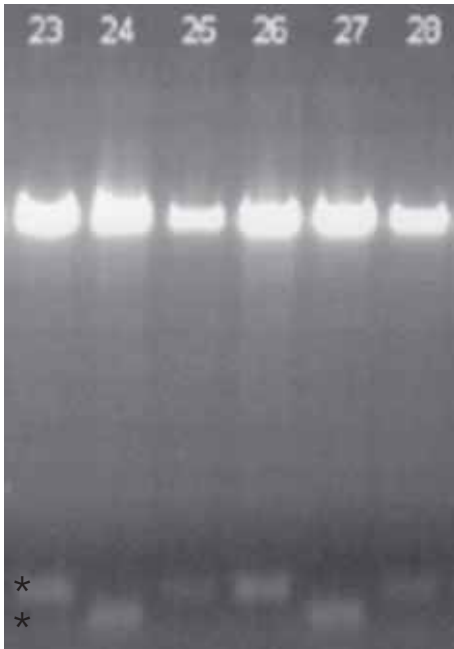
Tailor-made vector systems for the transduction of different cell types *in vitro* and *in vivo*.

Nanotechnology and biomedical research

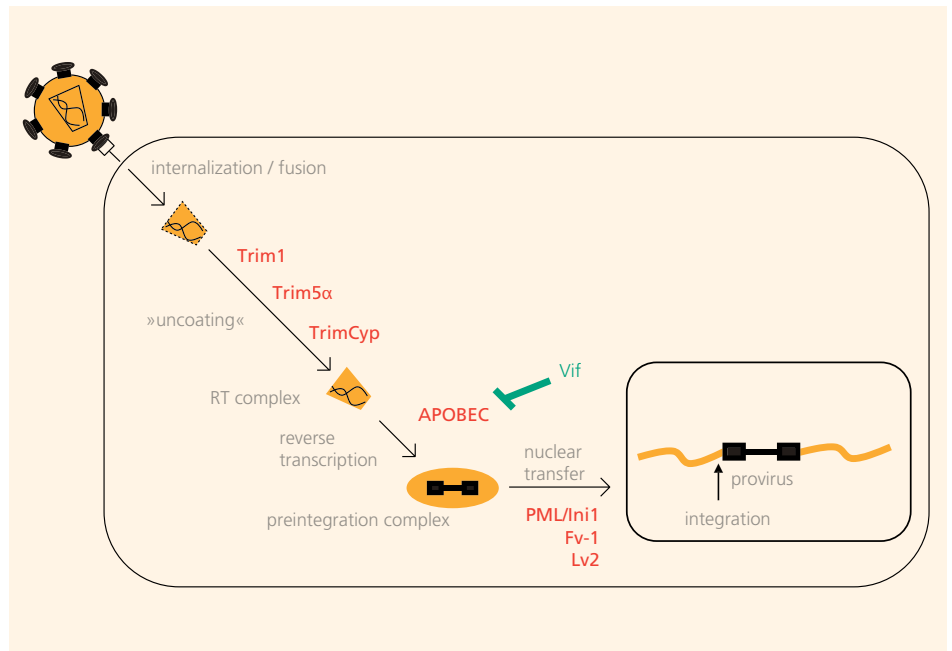
The use of nanomaterial for the development of new methods and tools in diagnostics and therapy.

Immune modulation

Specific modification of immune reactions.



Isolation of co factors (*).



Known intracellular restriction factors against retroviruses: In the framework of the innate immunity, restriction factors offer protection against retroviral infections by blocking the pathway of the virus inside the cell at multiple points. They restrict, for example, the uncoating or the release of the viral genome after penetrating the cell (Trim-proteins). Other factors cause hypermutation during reverse transcription of the retroviral genome into DNA (APOBEC). The viral protein, Vif, serves as a counterpart to APOBEC. If the generated viral DNA penetrates the nucleus of the infected cell, it will be integrated as a provirus into the cellular genome and thereby fixed in place. The transfer to the nucleus can also be inhibited by restriction factors (e. g. Fv-1). RT complex, reverse transcriptase complex.

Results

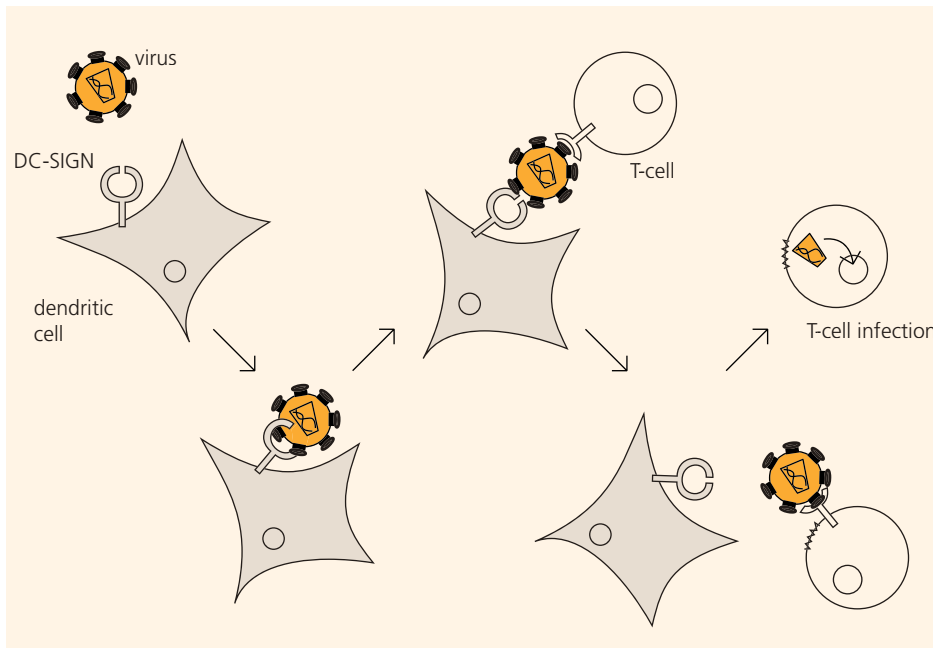
A genetic screening system for high throughput was extended to study intracellular defence mechanisms. This experimental concept was successfully used to identify a new cellular co-factor for HIV; this project was supported by the European Union. This unknown protein is now characterized and will be examined closely. The withdrawal of such a factor may be used to block or inhibit an HIV infection in the cell, before integration occurs.

In cooperation with the HIV Drug Resistance Program at the National Institutes of Health in the USA a further factor (mCPSF-6) was characterized. This factor inhibits HIV very efficiently. These proteins could represent promising targets for therapeutic interventions in the future, and therefore need to be tested now.

New nanomaterials were used to develop a kit, which enables the simple and straight forward isolation of HIV. This enables not only monitoring during therapy; the isolated virus can also be investigated in follow-up studies. This project was financed by the Stiftung Industrieforschung (Industry Research Foundation Grant).

Successful modulation of the T-cell response was achieved using regulatory T-cells that are antigen specific. This is a newly developed technology developed at IZI (world wide patent pending).

A specific modification of the T-cell response enables a specific modulation of the immune system. The possibilities and the potential of the technique developed at IZI are manifold and are currently under investigation.



Mucosal transmission of HIV (simplified illustration): HIV enters the organism via the mucosa. In peripheral tissue, immature dendritic cells are localized that express the receptor DC-SIGN. HIV binds to DC-SIGN and is “smuggled” by the dendritic cells into the lymph nodes. In the lymph node, the virus finds T-cells that express CD4 as well as co-receptors needed for a successful infection. The virus particles bound to DC-SIGN are presented to the T-cells. HIV interacts with the T-cells and now the virus can infect the T-cells very efficiently.

Potential

AIDS was first described more than 25 years ago and HIV is the most intensively researched virus world wide, and still the disease can not be cured. Successful antiviral treatment using a combination of drugs (HAART, highly active antiretroviral therapy) is able to suppress the virus population for some years; however a cure is not possible. This is due to the high mutation rate of the virus, which with time enables it to circumvent any treatment.

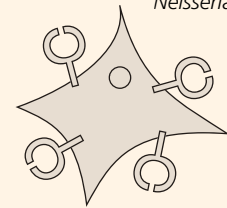
The development of a vaccine has failed. New treatment strategies are desperately needed to fight the AIDS pandemic. The interaction of the virus and its host however is highly complex. One critical aspect of this complexity is the interaction of the virus with intracellular defence mechanisms against pathogens that have evolved over millions of years of co-evolution. These may be used to trigger HIV resistance. A second aspect is co-factors that are used by the virus for its replication. Without these factors the virus can not replicate. Both classes of factors may be used for new strategies to fight pathogens. Targeting these cellular factors would mean targeting the virus’ counterpart.

Viruses:

Retroviruses
(HIV-1, HIV-2, SIV, FIV)
Cytomegalovirus
Hepatitis B and C
Coronaviruses
Filoviruses (Ebola)
Dengue Virus
Alphaviruses
Measles Virus
West Nile Virus

Bacteria:

Mycobacterium tuberculosis
Helicobacter pylori
Streptococcus pneumoniae
Neisseria meningitidis



Protozoans:

Schistosoma mansoni
Leishmania amastigotes,
pifanoi

Fungi:

Candida albicans
Aspergillus fumigatus
Ceratinophilic fungi

DC-SIGN, a C-type lectin on the surface of dendritic cells, binds a large number of pathogens. A selection of different pathogens that interact with DC-SIGN are shown.

A further focus of the laboratory is the mechanism of mucosal HIV transmission. The virus uses a cellular protein on cells patrolling the mucosa and hitchhikes on these cells to the lymph node where T-cells - the target cells for HIV - are present. To unravel this mechanism would allow the eventual prevention of an HIV infection. Prevention would be preferable to a therapy, which has proven to be very difficult once the virus was able to establish an infection in the organism.



Immunotherapy – Oncology Group

Contact

Dr. Christoph Schimmelpfennig
Phone: +49 (0) 341/355 36-3105
christoph.schimmelpfennig@
izi.fraunhofer.de

Competencies

- expansion techniques for different effector cell systems including cytokine-induced killer cells (CIK) (human and murine)
- tissue culture, cytotoxicity assays, cryoconservation
- molecular imaging facility, including bioluminescence / fluorescence imaging
- high speed cell sorting facility
- luciferase transgenic cell lines
- board certified doctor for internal medicine, hematology and oncology

- luciferase transgenic mice (Balb/C NFkB-Luc)
- luciferase based tumor and sepsis model
- FACS

A range of products and services of this group can be found on page 28-29.

Profile

The scientific focus of this group is the development of new therapeutic strategies in the field of oncology / hematology.

Project

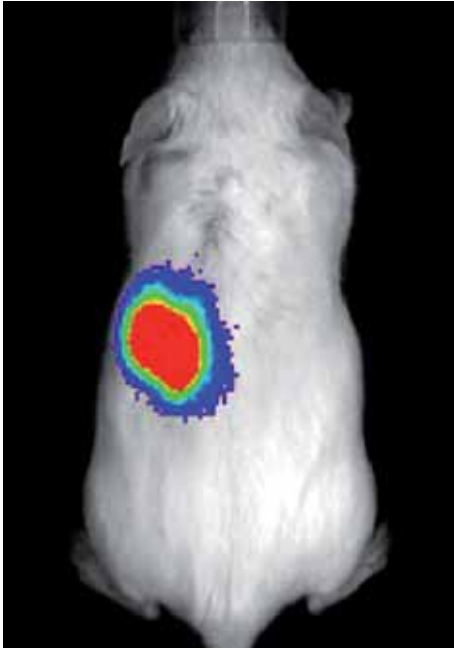
Background

Metastatic cancer has a poor prognosis in general. For example, in patients with metastasized gastric or pancreatic carcinoma, the median survival range is between one to two years. Curative concepts are still not available. Chemotherapy prolongs survival, but cannot cure patients. Also, chemotherapy can induce severe complications such as immunosuppression, fever, aplasia, nausea and loss of hair. Therefore, new therapeutic strategies are highly

warranted. Immunotherapy is attractive, because it reinforces the immune system of the patient providing the opportunity to suppress the malignant disease.

Aims

The aim of this group is the development and evaluation of new drugs and therapeutic strategies in the field of oncology/ hematology. This includes all necessary experiments starting from first experiments in tissue culture,



Visualization of a tumor growth through bioluminescence imaging.



Immunotherapy – Oncology Group (f. l. t. r.): Juliane Wagner, Dr. Christoph Schimmelpfennig, Ulrike Ehlert, Katja Landgraf, Moritz Weiher, Natalia Shurawel, Martin Bach.

studies in small animals, set up and optimization of techniques for mass production and the planning and performance of clinical studies.

Results

In the past year our group has established and optimized methods for production of human and murine Cytokine Induced Killer cells and Dendritic Cells. In addition we established test systems for determination of cytotoxicity of effector cells *in vitro* and *in vivo* using a variety of murine tumor models (e.g. a human colon cancer model for NOD SCID mice, a murine EL4 luc based lymphoma model and others). These mouse models are investigated primarily using Bioluminescence Imaging. In addition evaluation with CT scans or MRI is possible. Recently, a strain of transgenic mice in which the NFkB gene is linked to luciferase was established as an animal model for the investigation of pre-clinical questions in oncology and sepsis.

Potential

Using our new, innovative mouse and tumor models we are currently engaged in industry-directed applied research which concentrates on testing novel anti-cancer drugs and new therapeutic approaches for the treatment of malignant diseases. This research is being carried out in cooperation with scientific partners and on our own initiative

Special Background

Bioluminescence Imaging (BLI) has proven to be a very sensitive technique for visualizing the migration and survival of cell populations and the visualization of targeted gene activity in living animals. It allows the serial investigation of a single animal over an extended period of time and targeted histopathologic tissue sampling. BLI is based on the introduction of a reporter gene that encodes for the bioluminescent protein luciferase. The emission of bioluminescent light can be detected and the origin of the light source can be determined. In addition, multiple reporter genes emitting light on different wave lengths can be detected in an individual animal separately and provide further information about cell to cell interactions. Detection of BLI signals can be linked with *in vitro* assays.



Neurorepair Group

Contact

Dr. Johannes Boltze
Phone: +49 (0) 341/97 25-814
johannes.boltze@izi.fraunhofer.de

Competencies

- multi-modal system for evaluation of cell therapies in relevant animal models
 - unique large animal model for long-term evaluation of experimental stroke treatments
 - application of modern imaging techniques, also in combination
 - detailed histological and stereological tissue sample analysis
 - research according to STAIR criteria in stroke therapy development
- SNP-analysis in the human genome
 - close partnership with clinical stroke experts
- A range of products and services of this group can be found on page 28-29.

Profile

Our focus is on development of novel therapeutic approaches for ischemic stroke. In addition to cell culture experiments and molecular biology, specialized small and large animal models are used for behavioural and histological evaluation. Applied imaging techniques (MRI/PET) allow *in vivo* monitoring of regeneration. Furthermore, we investigate principle mechanisms of cerebral ischemia as well as the genetic basics of dyslexia.

Project: Stroke – Advanced Treatment Strategies Using Adipose Tissue Derived Regenerative Cells

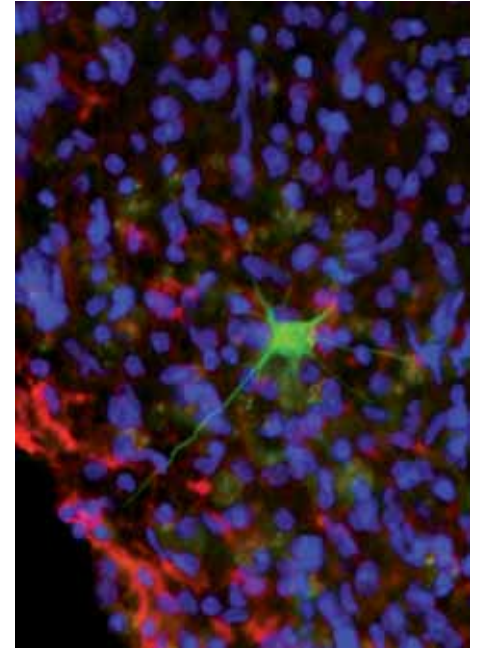
Background

Stroke is the third most common cause of death and the most important reason for permanent disabilities in adulthood. In addition to the significant impact on patient welfare and major socio-economic consequences, common risk factors are a major problem related to the disease. Despite vigorous research in the past decades, the only effective therapy for stroke

is thrombolysis. As the treatment is bound to a narrow time window of 4.5 hours, less than 10 percent of all stroke victims receive effective treatment. A regenerative cell population isolated from autologous adipose tissue by technology of Cytori Inc., San Diego is already under clinical evaluation for the treatment of myocardial infarction. These cells might help to improve recovery upon ischemic stroke.



Neurorepair Group.



Single nestin-positive cell (green fluorescence) situated in the border zone of an ischemic lesion. Nuclei are stained blue (DAPI). Red fluorescence indicates GFAP, a marker protein for reactive astrocytes. These cells form the glial scar engulfing the lesion core.

Aims

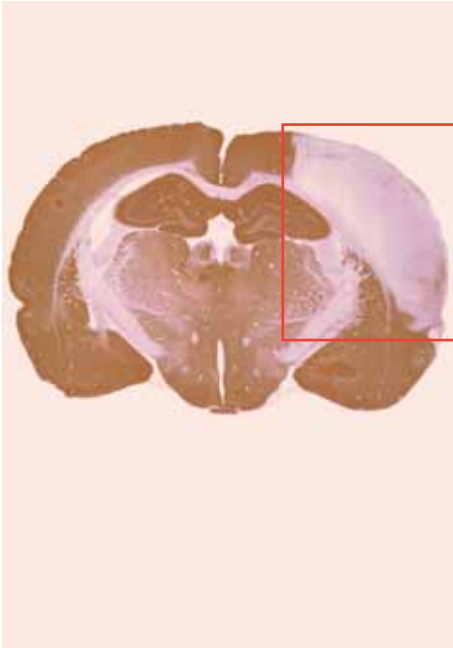
The Neurorepair research group received the task to ascertain the efficacy of Cytori's regenerative cells following focal cerebral ischemia. The application of the rigorous STAIR criteria was defined as essential for the entire project. These criteria, periodically published by an international expert board, are of extraordinary importance during the preclinical development of stroke therapies. The Neurorepair research group will investigate the therapeutic impact of Cytori's regenerative cells in different concentrations and at various time points in two small animal models. Subsequently, results will be confirmed in a large animal trial. In addition to behavioural phenotyping and detailed immunohistology, MRI and PET imaging will be crucial for the monitoring of regeneration during the project.

Results

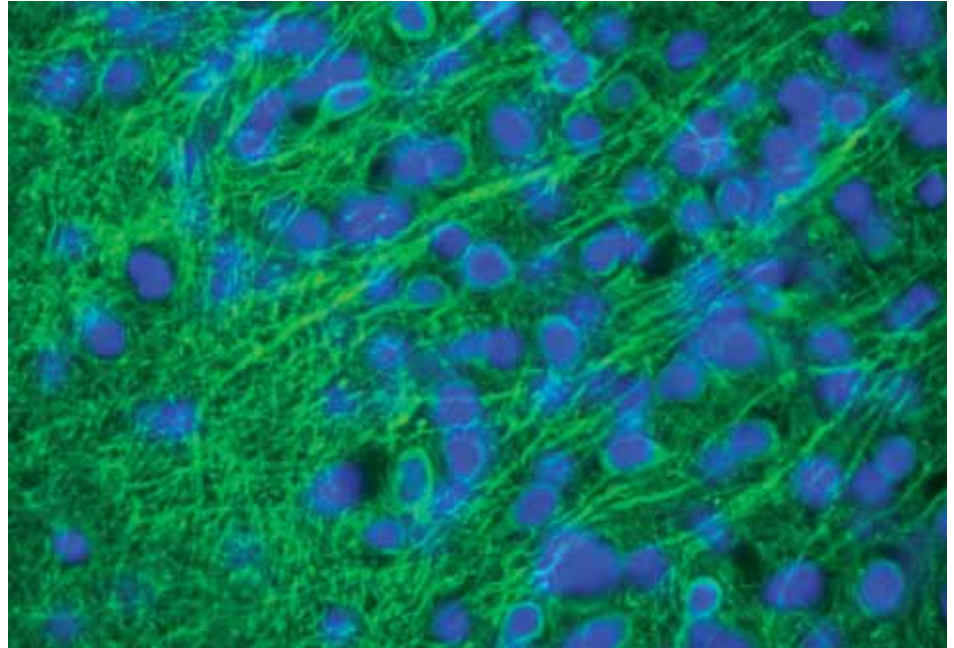
In the first step, the patented Cytori isolation technique for regenerative cells from autologous adipose tissue was established at the Fraunhofer IZI. Restrictive parameters for process quality assessment and monitoring were introduced and will be applied throughout the entire project. Within a few weeks, two parallel, completely blinded trials were initiated in a specialized rat model. The first large animals were also included in a preliminary test cohort. Repeated imaging and continuous assessment of functional recovery based on behavioural tests are used for evaluation of the results.

Potential

After confirming the therapeutic efficacy of stroke treatment by regenerative cells, all STAIR quality assurance criteria will be met in subsequent trials and experiments. This is of primary importance for the translation of the therapeutic concept from an experimental stage into a clinical trial and will be crucial for the process of future decision-making regarding such endeavours by regulatory authorities. The evaluation of a novel cell-based stroke therapy with the unique large animal model maintained of Fraunhofer IZI will be performed for the first time in contract research for the development of stroke therapy.



Brain damage image following permanent occlusion of the right middle cerebral artery.



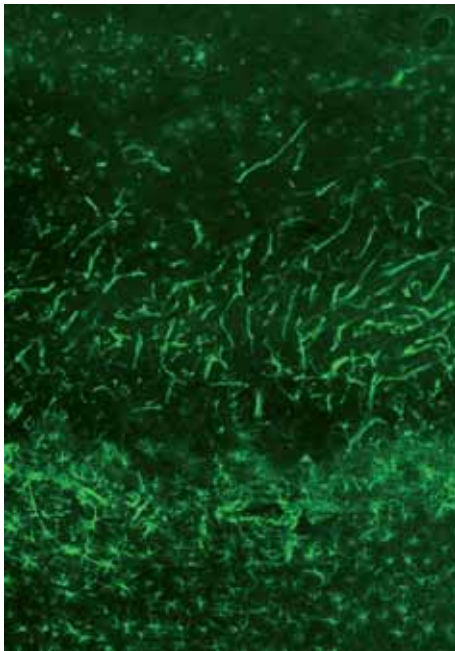
Neuropil in healthy rat brain – representation by microtubuli-associated proteins. Nuclei are stained in blue (DAPI).

Further Projects

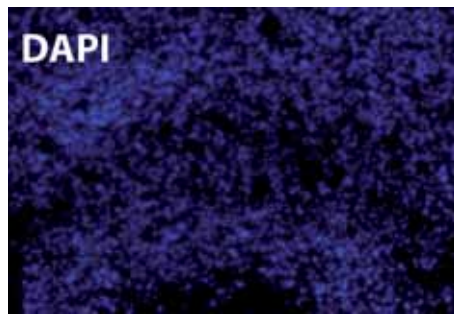
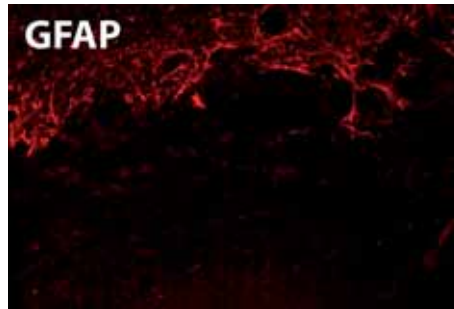
The Neurorepair research group also evaluates the age-dependency of regenerative effects after administration of various adult stem cell containing populations. Both the age of the cell populations and that of the experimental subjects are taken into consideration (ADUCCELL). Further projects elucidate possible synergistic mechanisms of stem cell combinations (SIRIUS). A BMBF-project (MARS) deals with the proof-of-principle of a combined pharmaceutical-stem cell approach targeting different regenerative mechanisms.

The PLUTO project will elucidate the genetic basics of dyslexia in order to design a diagnostic kit for the disease.

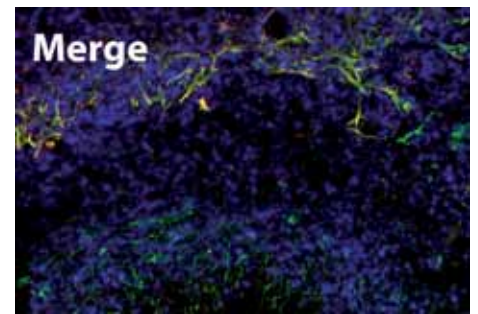
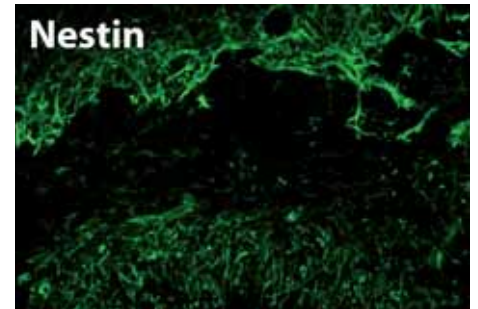
Our group has also arranged an educational service project for large animal surgery and has supported two large animal trials in cardiac surgery with up to three veterinarians who are responsible for peri-surgical care and anaesthesia.



Reactive astrocytosis and vessel regrowth at the border zone of the cortical ischemic defect.



Border zone of ischemic lesion in the cortex. GFAP, a marker of reactive astrocytes is visualized in red. Green fluorescence indicates proliferating cells, of which some have stem cell properties. Nuclei are stained blue (DAPI).





Stem Cell Technology Group

Contact

Prof. Dr. Nicole zur Nieden
Phone: +49 (0) 341/355 36-3305
nicole.zurnieden@izi.fraunhofer.de

Competencies

- *in vitro* screening models
- embryo toxicity and teratogenity
- substance testing under REACH
- bioreactor technologies
- technologies for embryonic and early stem cells
- signal transduction pathways and target gene activation
- reporter ES cell lines for target gene verification

- *in vivo* models for bone regeneration

A range of products and services of this group can be found on page 28-29.

Profile

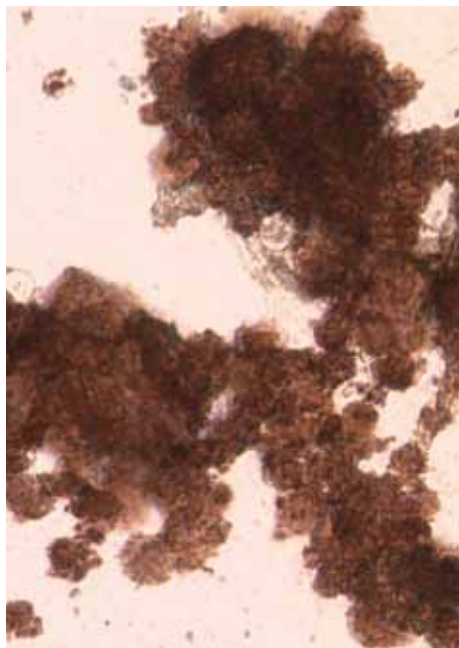
Targeted intervention in the complex events of tissue regeneration has appeared to be technically unachievable for the past decades, yet novel insights have raised hopes of the possibility to direct the potential of pluripotent stem cells for specific use in medical treatments and drug screening. This group develops high-throughput culture methods for stem cells and optimizes strategies for the differentiation of these cells into diverse mature cell types.

Project: Pluripotent Stem Cells in Automated Prediction of Toxic Influences on Bone Development

Background

Birth defects are the leading cause of death of newborns. Congenital anomalies may be attributed to pharmaceuticals when administered during pregnancy. The initial goal of early drug development programs is therefore to include animal studies to exclude developmentally toxic side effects. Here, existing *in vitro* tests are rarely definitive as they demonstrate a low prediction potential and bring immense costs with them.

Due to their unlimited self-renewing potential and their multilineage differentiation potential, embryonic stem cells (ESCs) represent a potential bottomless source for preclinical screening of pharmaceuticals. ESCs are routinely used in industry in the context of the embryonic stem cell test (EST), which was evaluated to be superior to other known *in vitro* assays in an international validation study. However,



“Von Kossa” staining for mineralized calcium. Embryonal stem cells are differentiated to bone cells with vitamin D3, vitamin C and a phosphate source. Matured bone cells are seen as brown / black.



Stem Cell Technology Group: (f. l. t. r.) Prof. Dr. Nicole zur Nieden, Susanne Trettner, Huawen Ding, Susann Horvat, Beatrice Kuske, Anke Dienelt, Dr. Vuk Savkovic, Alexander Seeliger, Dorota Kaniowska.

one of the limitations of the EST is that the only endpoint is cardiomyogenesis, and there is no metabolising system or automation.

Aims

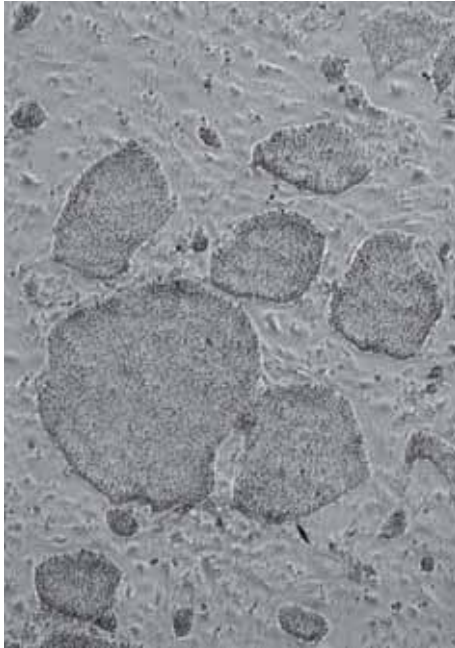
Approximately half of the current animal studies are conducted to evaluate the osteotoxic potential of new chemical entities. The goal of the research program is to provide the industry with a functional automated *in vitro* osteotoxicity test that can routinely be used to screen compounds before they are introduced to the market or to evaluate existing ones.

The acceptance of an *in vitro* test in industry is dependent on three variables: the test must possess a high predictive potential, it must be inexpensive and it must have short assay duration. Our group foresees the development of automated osteotoxicity models by using ESCs for the prediction of bone

development harming substances. This shall be accomplished by shortening the assay duration to raise commercial attractiveness and the use of a primate ESC line and human multilineage progenitor cells (MLPCs) to increase predictivity with minimal human handling.

Results

The group has several years of expertise in the area of directed differentiation of stem cells. Protocols for the directed differentiation into of murine ESCs into osteoblasts have been established in 2006 and have now been successfully transferred to primate ESCs in the first step of this project. Additionally, human multilineage progenitors generally also respond to differentiation induction using our standard protocols with initiation of osteogenesis. However, due to their longer population doubling times and senescence in culture, it will be difficult to generate cells in adequate numbers and adequate time for inoculation of bioreactor vessels. In the near future, studies will follow to further enhance the differentiation efficiency and characterize appropriate endpoints. Initial toxicological data are soon to be expected.



Embryonic stem cells from the common marmoset monkey (*Callithrix jacchus*) are kept in the pluripotent state on a so-called feeder layer of embryonic mouse fibroblasts with the addition of basic Fibroblast Growth Factor.



Bioreactor for the expansion of stem cells.

Potential

The introduction of new endpoints will lead to the shortening of the assay duration, whereby costs are lowered and the attractiveness of the assay for industry is raised. Based on the incorporation of primate cells the predictivity of the test will further increase. The goal is to completely substitute *in vivo* osteotoxicity studies with the automated *in vitro* assay.

Special Background

Definition of Stem Cells

All types of stem cells are described using two characteristics: their capacity for self-renewal and their differentiation potential.

Capacity for Self-Renewal

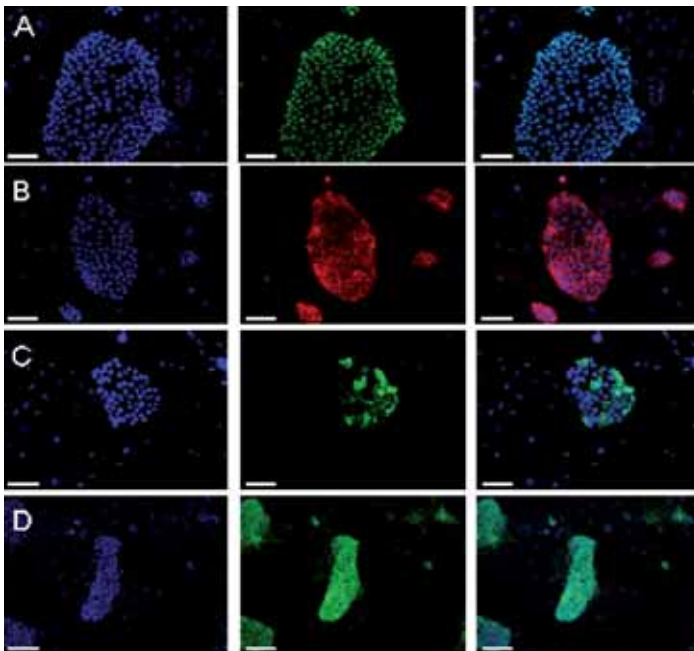
Stem cells have the potential to continually produce daughter cells that retain the same characteristics as the original cell. This daughter cell capacity occurs through asymmetric division, on the one hand daughter cells with stem cell properties and on the other hand differentiated daughter cells are produced.

Capacity for Differentiation into Specialized Cell Types

Stem cells are somatic cells that are not yet differentiated. This means that they are not yet in a form that specializes them for use in the organism.

Types of Stem Cells

Stem cells are primarily distinguished by their age and potential for differentiation: the ontogenetically earliest stem cells are the totipotent embryonal stem cells from which the primitive germ stem cells as well as the somatic stem and progenitor cells arise, which one finds in nearly all tissues of the adult body.



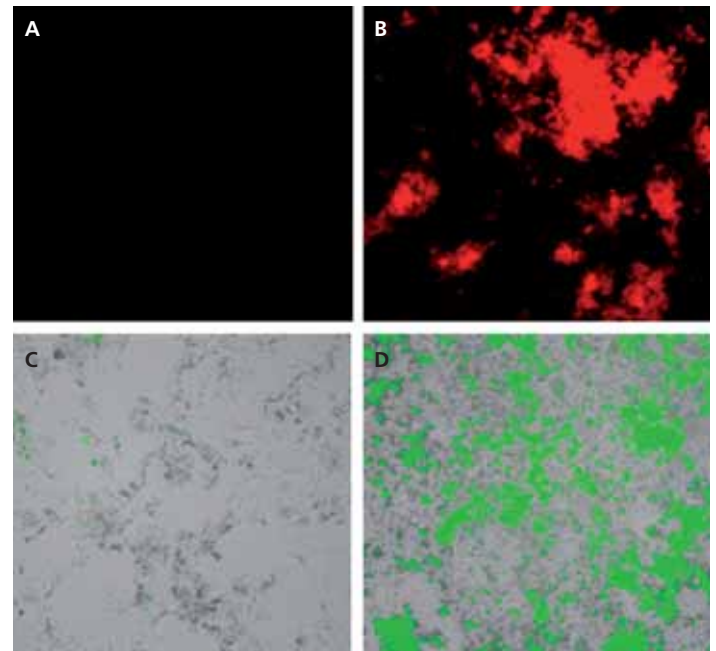
The pluripotency of Callithrix ESCs is periodically tested with antibody staining.

Left: nuclear staining with DAPI.

Middle: (A) Oct4; (B) SSEA4; (C) TRA-1-60; (D) CatnB.

Right: overlay.

Bar = 100 μ m.



Differentiated Callithrix ESCs. (A) and (C) control media, (B) and (D) osteoinduction media. Mineralized bone cells are made visible with Alizarin red staining. Newly synthesized matrix stores tetracycline which is autofluorescent and therefore the bone cells can be visualized. Notably, fluorescent cells can only be seen in osteoinduction media.



Stem Cell Biology Group

Contact

Dr. Alexandra Stolzing
Phone: +49 (0) 341/355 36-3405
alexandra.stolzing@izi.fraunhofer.de

Competencies

- aging research: evaluation of cell aging, manipulation of cell aging
- stem cell biology
- reprogramming
- cryoconservation

A range of products and services of this group can be found on page 28-29.

Profile

The group combines insights from stem cell biology and biogerontology to develop novel strategies in regenerative medicine. We pursue a variety of innovative methods to “rejuvenate” adult stem cells *in vitro* and *in vivo* so that these cells can resume their function as promoters of regeneration, particularly in elderly patients.

Project: Mass Customized Organ Replicates – Tissue Engineering on Demand

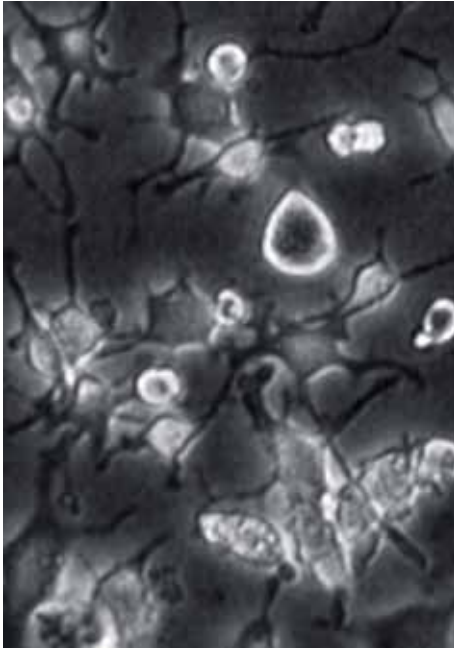
Background

The production of functional organs such as the liver, via tissue engineering is still not possible, as basic questions such as vascularisation of the tissues have not been satisfactorily answered. In this project we will develop an automatic system for the tissue engineering of skin, which represents a simple model tissue. New solutions for tissue engineering problems will hopefully be solved in this project.

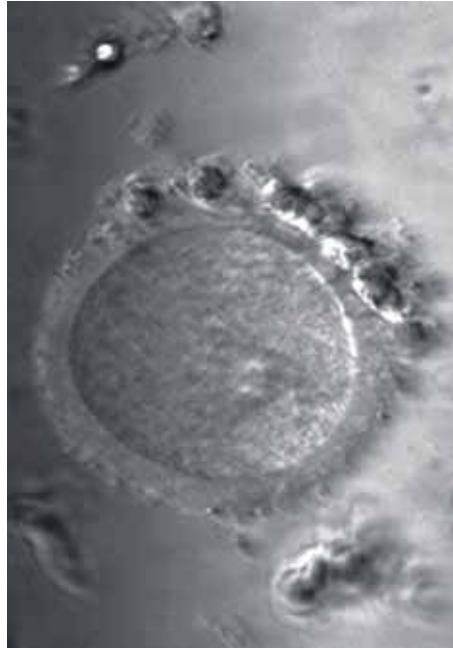
Tissue-engineered skin can be used for transplantation or for *in vitro* toxicity assays. In these tests substances are analysed for their damaging effects upon skin. This can be used as an replacement or in addition to animal testing.

Aims

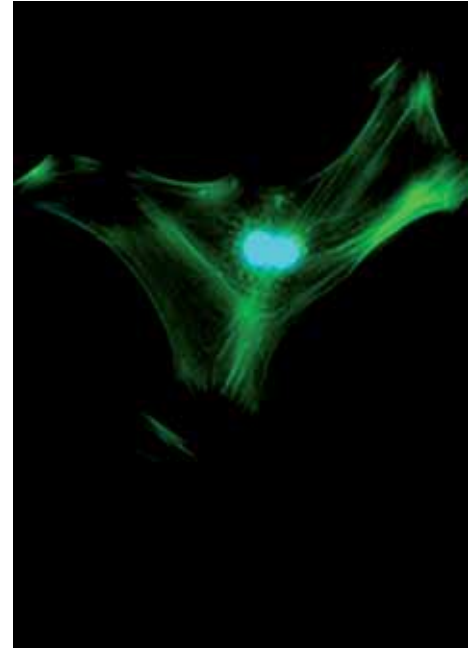
The first goal in this project is the production and testing of human non-viral induced pluripotent stem cells (iPS) for the automatic production of skin. The second goal is the cryopreservation



Differentiated microglia of mice stem cells.



Mice oocyte for partial reprogramming.



Cell fusion as a subject for study of cell reprogramming.

Special Background

Induced Pluripotent Stem Cells (iPS)

Induced pluripotent stem cells are derived from cells of the human body and are reprogrammed in the lab. As the production of iPS cells is ethically unproblematic, the use of these cells is especially important for countries with very restrictive laws, such as Germany. At the moment our group has pro-

duced these cells using the non-viral transfer of genes, inducing a pluripotent status. These cells can then for example be differentiated towards a keratinocyte fate. We have furthermore developed within our project iPS cells which have not been derived using any viral components. The potential of

these cells is vast, however we still have much to discover about these cells. The research area induced pluripotent stem cells was recently named the "greatest scientific advancement in the year 2008" as voted by the scientific journal Science.

of cells used for future skin production. The storing of cells for skin tissue engineering provides the opportunity of reacting to future changes in market demands.

In the moment most cryo-solutions contain dimethyl sulfoxide, a toxic substance, one of our goals is the replacement of this substance. In addition we will replace the serum of the cryo-solution to be able to use the solution in cell transplantation settings as well. The goal is to maximise the survival rate of the cells and preserving stem cell characteristics.

Results

The first non-viral reprogrammed human IPS cells, derived from fibroblasts and mesenchymal stem cells have been produced and have now been analysed in detail. Our group could demonstrate that these cells expressed pluripotency markers and had an morphology resembling human embryonic stem cells.

Furthermore our group has developed novel solutions for the cell cryopreservation of human keratinocytes and fibroblasts, with increased cell survival following cryoconservation.

Potential

Our group is currently engaged in increasing the speed of the production of IPS cells and in the creation of stable cell lines derived from these IPS cells. These cells will then be used in the automatic production of skin models. We will also further improve the cryo-solutions and test alternative temperature protocols for cryopreservation. The protocols derived from this project will then be integrated into the automated skin production system.



Cardiorepair Group

Contact

Dr. Alexander Deten
Phone: +49 (0) 341/355 36-3505
alexander.deten@izi.fraunhofer.de

Competencies

- small animal surgery
- functional and molecular analyses
- cardiophysiology
- measurements of right and left heart function (ultra-miniature tip-catheter, echocardiography)
- cell labeling, immunohistochemistry
- analysis of gene and protein expression

A range of products and services of this group can be found on page 28-29.

Profile

The goal of this group is the development of cell-based and cardioprotective therapeutic strategies for ischemic heart disease. The effectiveness of these strategies in regards to relevant functional parameters and the underlying mechanisms are studied in *in vivo* models of myocardial infarction, ischemia / reperfusion and ischemic preconditioning in small animals.

Project: Cell Based Therapy of Ischemic Heart Disease

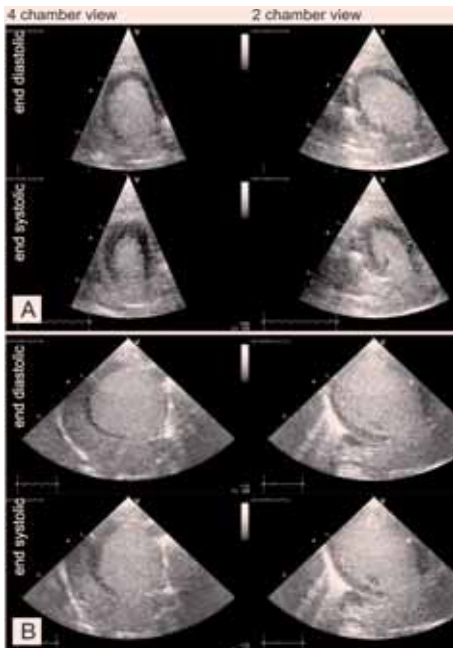
Background

Heart disease, particularly coronary heart disease and myocardial infarction are leading causes of death worldwide. Despite a high mortality following acute coronary artery occlusion, the irreversible loss of cardiomyocytes and the resulting process of cardiac remodelling leads to progressively reduced cardiac pump function and ultimately heart failure. The acute mortality after myocardial infarction has decreased

in the past decade due to improved early recognition and timely initiation of therapy. There are, however, only limited therapeutic options available to effectively treat impaired heart function and developing heart failure.

Aims

The group aims to develop cell-based therapeutic strategies for ischemic heart disease in small animal models of myocardial infarction and ischemia/reperfusion injury. Furthermore, the



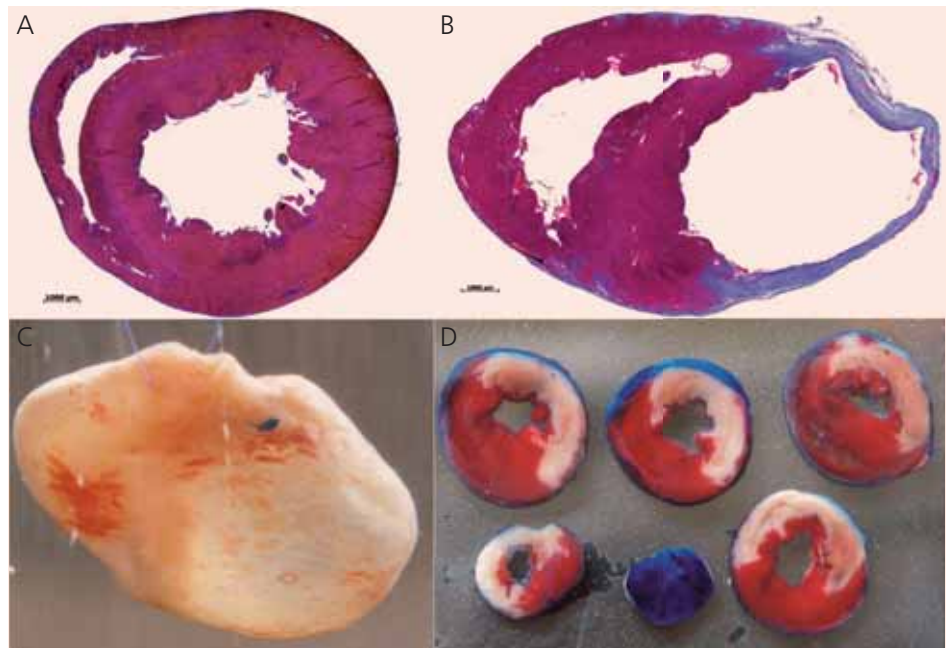
Echocardiographic measurement of heart function after contrast medium injection in apical 4-chamber (left) and 2-chamber view (right) 12 weeks after sham operation (upper panels) or myocardial infarction (lower panels) in rats.

underlying mechanisms are studied in order to enhance and optimize the treatment process and to improve cardiac pump function.

Results

An experimental system has been designed to apply any cell product or cardioprotective agent to study their effectiveness regarding relevant functional, cellular, and molecular parameters in *in vivo* models of ischemic heart disease in small animals.

The data indicate that the effects of cell therapy are predominantly mediated by paracrine mechanisms and cellular interactions. Furthermore, cell specific factors as well as timing and route of application have a major impact on effectiveness of cell therapy. However, extensive cardiac regeneration was not



Histological analysis of rat hearts (Masson's trichrome; blue = collagenous infarct scar) 8 weeks after sham operation (A) or myocardial infarction (B) induced by permanent coronary artery occlusion. Mouse heart 4 weeks after coronary artery ligation (C). Visualization of injured myocardium of rat heart through TTC staining (white = ischemic area; red = vital myocardium) after ischemia for 60 minutes and subsequent reperfusion for 24 h (D).

observed after local or systemic application of different cell populations. Further studies aim to continuously improve the treatment protocol and to specifically target the cardiac remodeling process after ischemic injury.

Potential

The applied *in vivo* models of ischemic heart disease build the basis for further research into the mechanisms and effectiveness of a variety of cell-based and cardioprotective therapeutic strategies. Moreover, they can be utilized to analyze new drug delivery technologies and to test different diagnostic and therapeutic markers.

Further Projects

In further studies, cardioprotective mechanisms and ischemic preconditioning are investigated as well as strategies for the effective application of cardioprotective agents. The goal of these experiments are to provide the cardiomyocytes with protection from ischemic or stress-induced injury.

Furthermore, differentiation of murine embryonic stem cells into cardiomyocytes is induced *in vitro* for further *in vivo* application. Along with isolated adult cardiomyocytes, these cells can be used to test the effects of cardioprotective agents as well as the toxicity of various substances.



Tumor Stem Cells Group

Contact

Dr. Peter Ruschpler
Phone: +49 (0) 341/355 36-2605
peter.ruschpler@izi.fraunhofer.de

Competencies

- immunological separation (MACS-bead, cell sorting) and characterization (FACS analytic) of primary cells and cell lines
- flow cytometry: FACS analytic
- test platform for the testing of sensitivity of tumor stem cells
- mixed lymphocyte cultures: MLTC (tumor stem cells vs. CD8+ T-cells)
- development and production of donor lymphocyte concentration

- EliSpot assay: functional representation of specific immuno reactivity
- ^3H thymidine proliferation assay
- ^{51}Cr release assay: cytotoxicity testing
- chemotherapy in animal model
- SCID mouse model

A range of products and services of this group can be found on page 28-29.

Profile

The objective of the group is to develop therapeutic strategies for the treatment of neoplastic disease which are based both on living cells as well as on pharmaceutically active ingredients. The foundation for these approaches is the elimination or modification of tumor stem cells (TSCs) in the targeted malignancy. Using the TSC concept, further TSC should be described and therapeutic innovations in the field of internal oncology will be made possible.

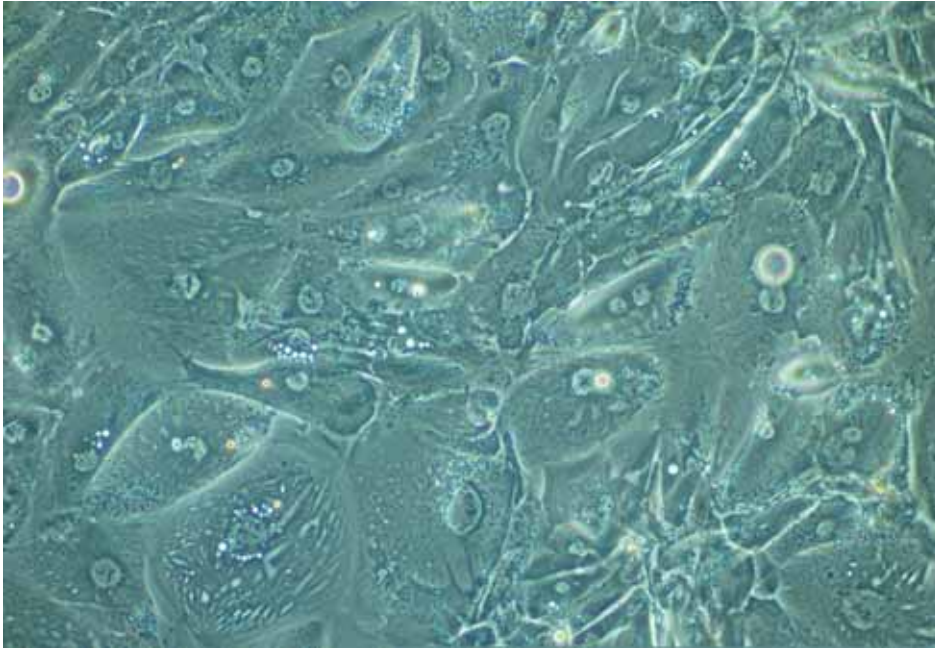
Project: New Approach for Cancer Therapy Through the Targeting of Tumor Stem Cells

Background

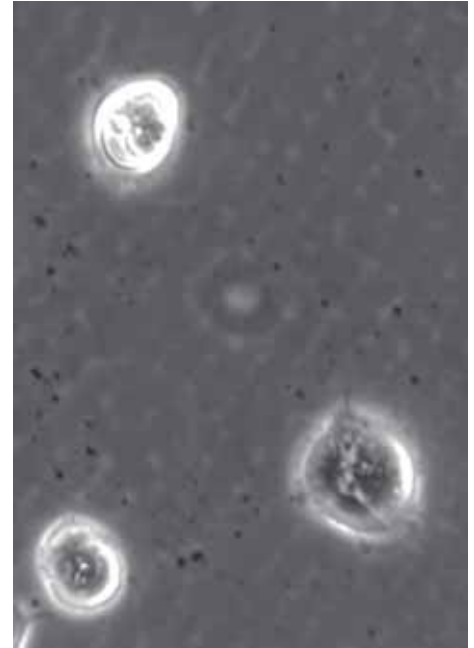
Up to the present day, adjuvant chemotherapy – along with surgery – has represented the focus of treatment strategies for countless neoplastic malignancies. However, advanced phases of various solid tumors often remain resistant to conventional treatment using cytostatic drugs and radiation. Therefore, new methods have recently been developed which target the molecular

mechanisms of a malignant conversion as well as tumor progression.

There is a small population of cells inside a tumor -- the tumor stem cells, which divide asymmetrically and which constantly renew the tumor by means of their own self-renewal. This theory is reinforced by the fact that a malignant neoplasm results due to the accumulation of multiple mutations in a single



Neoplastic tumor cell line of the renal cell carcinoma with typical cobblestone architecture.



Non-adherent tumor stem cells (TSC) from a breast carcinoma.

cell, sometimes over a period of several years. Since stem cells represent the only long-living cells in many kinds of tissues, they are the natural candidates in which early transforming mutations could accumulate.

Aims

This project is aimed at investigating the cytotoxic and cytostatic properties of various pharmaceutical agents. Using a specific cell-finding mode for tumor stem cells, breast, ovary and kidney carcinomas will be addressed. Due to the self-renewing properties and the specific accumulation of mutations within a TSC entity, these form the foundation for *in vitro* investigations for the development of innovative pharmaceuticals. The subsequent animal experiments, analyzing the absorption and retention of the tested substances, will form the second step of the project, which will be introduced by an initial tumorigenesis in the mouse, using the corresponding tumor stem cells.

The objective of the research associated with the project consists of the development of a standardized testing procedure (testing platform) which represents the cytostatic potential of new therapeutic agents with respect to specific TSC populations.

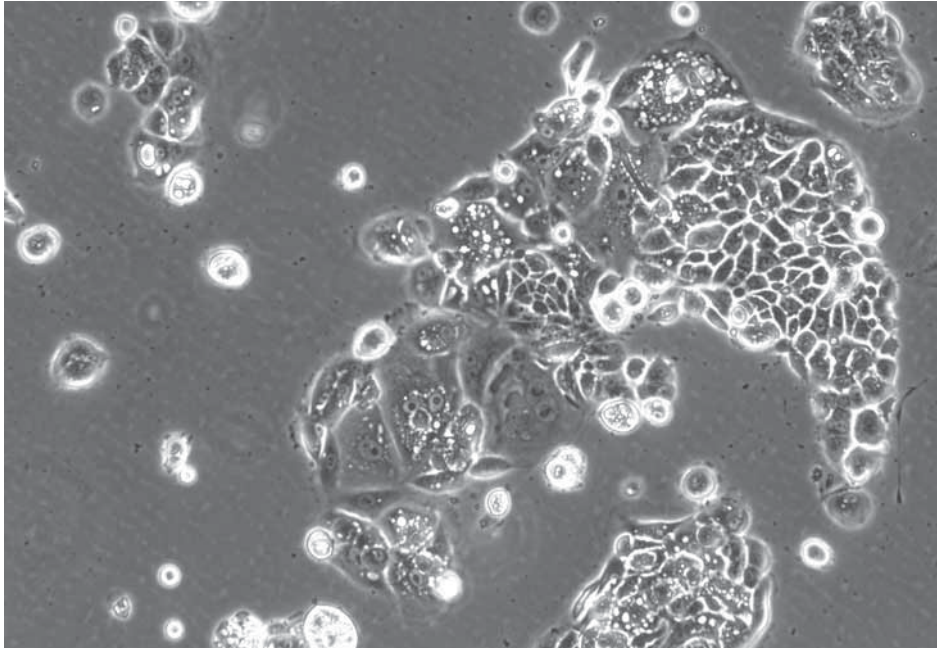
The targeted procedure will be developed with the goal of high specificity as well as economy with respect to time and expense.

In this context, a testing procedure for the identification of new cytostatic active agents is additionally to be developed, the cell-finding potential of which will contribute to attaining a highly selective cytotoxicity with respect to the TSCs of the corresponding tumor entities.

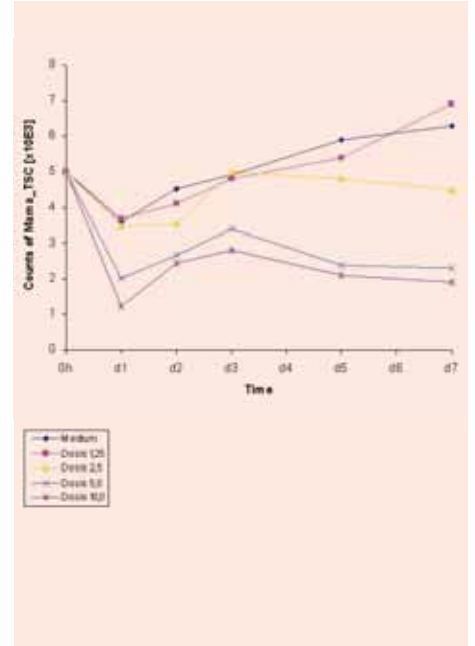
Results

The following results have been achieved since the work group was founded (June 2008):

- 1) reprocessing of 14 breast cancer explants – sampling after surgery – into primary cultures and the resulting establishment of three immortal breast cancer cell lines
- 2) isolation and cultivation of breast cancer TSCs from individual cell suspensions of the primary culture
- 3) testing of the cytotoxic effect of the substance ACD-101 on breast cancer tumor stem cells
- 4) flow-cytometric characterization of tumor stem cells of renal cell carcinoma
- 5) expansion of TSC-specific CD8⁺-CTL for the further production of therapeutic donor lymphocyte concentrations
- 6) sensitivity investigation of TSCs from breast, ovarian, and renal cell carcinoma with respect to the active agent candidate RP-101



Sphereoid formation of TSC of a breast cancer cell line.



Dosage dependent reduction of breast TSC by radioactive active agents.

- 7) production and description of a conditioned medium of the renal cell carcinoma line RU_RCC_001
- 8) flow-cytometric characterization of mesenchymal stem cells following manipulation of the conditioned medium RU_RCC_001

Potential

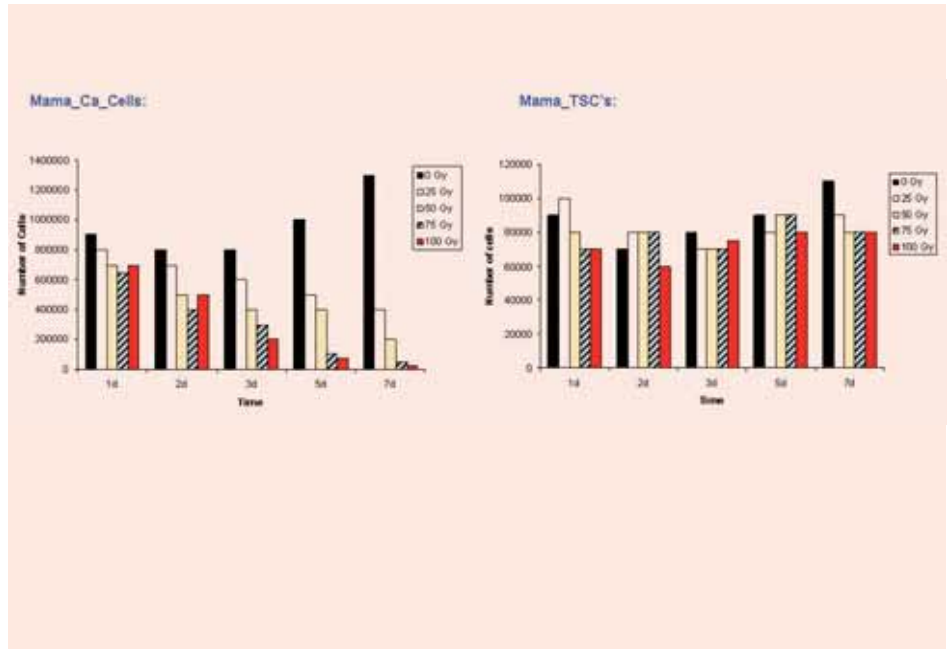
The focus of further investigations will be the identification, isolation, characterization, and expansion of undifferentiated tumor stem cells of various tumor entities. One initial target will be the development of a testing platform as a scientifically commercialized service in which the TSC lines – within optimized testing systems – of commercial partners are to be made available for the development of innovative active agent candidates.

Another focus of the scientific work is the investigation of medicinal and cell-based (CD8+-CTL) intervention on tumor-specific TSCs. In this context, cell cultures will be developed which reveal antigens associated with tumor stem cells. This will be carried out via the co-cultivation of the tumor stem cells of a tumor entity with exactly corre-

sponding, tissue-specific donor lymphocytes (mixed lymphocyte tissue culture; MLTC). Following an “immunological characterization phase”, CD8+ cytotoxic T-cells will be obtained. The result is a tumor-stem-cell-specific cytotoxic CD8+-T-cell line which can be applied in the screening of antigens associated with tumor stem cells and for tumor intervention.



Establishment of a tumor stem cell specific CTL against breast CA (IFN- γ -ELISPOT-Assay).



Reduction of the breast cancer cell line with a radioactive candidate drugs.

Special Background

In the context of a breast-preserving therapy, a lumpectomy accompanied by the application of hormonal therapy and adjuvant chemotherapy represents the focal point of treatment strategies for breast cancer.

However, the advanced phase of breast cancer remains resistant to conventional cytostatic and radiation treatment.

For the development of innovative forms of therapy, knowledge must be obtained regarding the internal connectivity between progression, remission and recurrence of a tumor as well as regarding the correlation with the existence of specific tumor stem cells. Tumor stem cells represent a very small cell population within a tumor which is able to renew itself and, thus, to maintain tumorigenesis.

A TSC population can be defined by three observations:

- 1) Only a minority of tumor cells are "tumorigenic" = TSC (ca. 1 - 10 percent).
- 2) TSCs carry specific surface markers and can, thus, be isolated from the whole tumor via immunoselection.
- 3) Tumors grow out of TSCs and reproduce the complete phenotypical heterogeneity of the parental tumor, since they can resist conventional therapies (cytostatic/radiological).



Vascular Biology Group

Contact

Dr. Andreas Schubert
Phone: +49 (0) 341/355 36-5105
andreas.schubert@izi.fraunhofer.de

Competencies

- microbiology of aerobic and anaerobic bacteria
- cultivation of cariogenic bacteria in biofilms under *in vitro* and *in vivo* conditions
- flow mechanics (rheology) and flow testing system
- technologies for the determination of genetic expression profiles

A range of products and services of this group can be found on page 28 - 29.

Profile

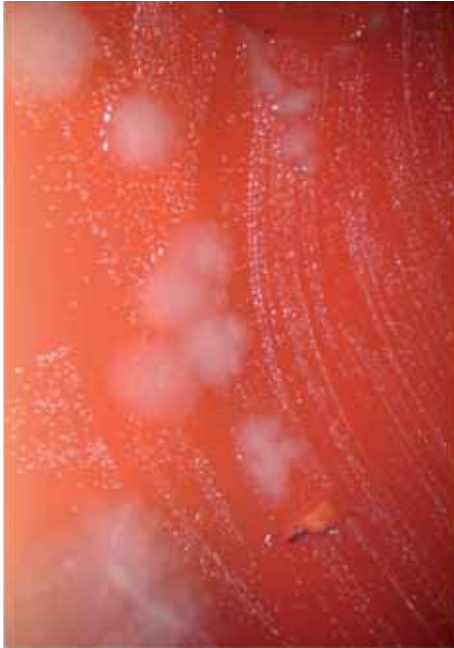
The goal of this group is the development of a preventative and at least partially curative gene therapy for arteriosclerosis. Using vascular models, genes and promoters are identified that can be activated by biomechanical forces such as flow or stretching. Because cardiovascular disease is often induced by dental disease (caries, periodontitis), a second focus of the group is in the establishment of a therapy against oral streptococcus.

Project: Antimicrobial Peptides to Fight Periodental Disease

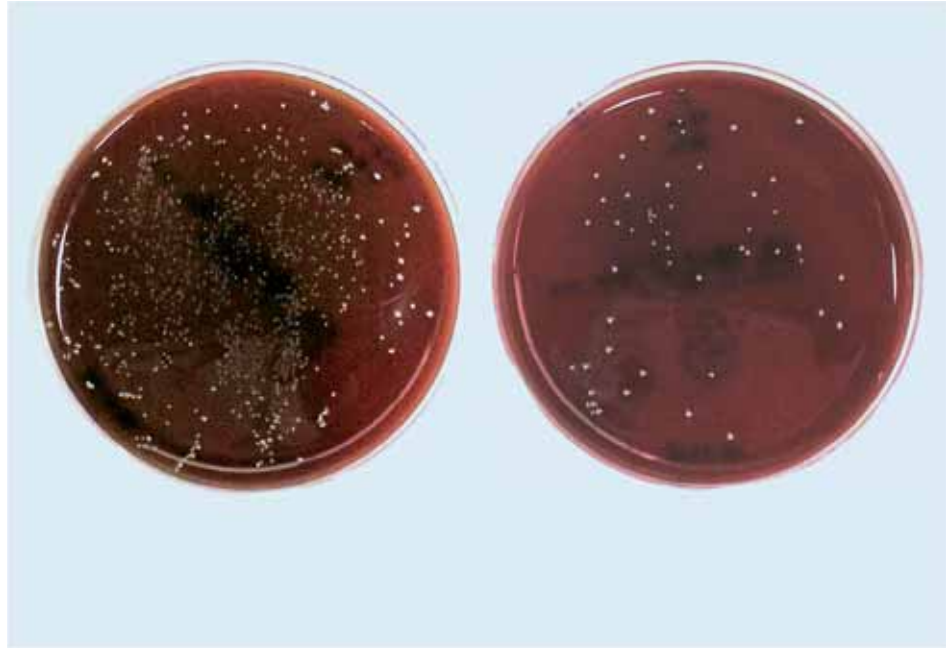
Background

Periodontal disease (caries or cavities) is the most common infectious disease in the western world. According to WHO 2004 estimates, 80 percent of the world population and 60-90 percent of school-age children (varies with the countries) have caries. Over 95 percent of the population alone in Germany have dental caries. Only 0.8 percent of the German population have a healthy primary dentition. Of children aged 12-

60 months 5-15 percent (35 percent in the lower socio-economic classes) suffer from Nursing-Bottle-Syndrome. Dental caries treatment cost the Health Insurance companies 24 billion German Marks in 1997. And that is without taking the patients' costs into consideration. This makes dental caries one of the most cost intensive infectious diseases. The development of more cost-effective caries therapies would therefore be considered a break-



AMP producing colonies dissolving *streptococcus-mutans* colonies.



Control cells after 12 hours incubation without additional anti microbial peptides (left) and *streptococcus-mutans* colonies after incubation with the supernatant of AMP producing bacteria after 12 hours incubation.

through, given the precarious financial situation of the public health insurance companies. It is important to note that oral bacteria often lead to the aggravation of other likewise very cost intensive diseases (arteriosclerosis, calcification of the heart valves, etc.).

Aims

The Vascular Biology work group has developed systems and processes to test the various kinds of oral bacteria that cause caries and periodontitis. This development was carried out in cooperation with the clinic for conserving odontology. The aim of this ongoing project is to establish rat models and to demonstrate their validity under *in vivo* conditions. At this stage three different independent methods for the specific (targeted) combat against cavity-causing bacteria will be developed as the main objective. In addition the interaction of special aggressive types of *Streptococcus mutans* and *Streptococcus sorbrinus* with tooth enamel was investigated. Furthermore, the analysis of the effects of these patho-

genic germs and the apathogenic germs of the mouth flora seems to be consequential for the understanding of the formation and progression of caries and periodontosis. The starting point for the investigation of cavity-causing microorganisms is the establishment of a method for mass spectrometric analysis of oral biofilms. The single spectra on isolated single colonies whose identity was determined through sequencing of their 16S rRNA was entered in a database. The database provided a basis for obtaining information about the relationship between special aggressive dental disease progression (manifestation) such as caries and periodontal disease and a specific oral protein pattern.

Results

Many different antimicrobial peptides which were tested for oral streptococcus were isolated. Furthermore two independent sequence libraries were developed which contain sequences of billions of different potential antimicrobial peptides. Both eukaryotic and prokaryotic expression systems were used to prevent that the lethal effect of the antimicrobial peptides kills the expression host.

Potential

Continuation of the ongoing research is scheduled for next year. Currently, experiments on cloning have begun with the aim of identifying the antimicrobial peptides, which are capable of killing specific periodontal pathogens and microorganisms. This would be the first milestone in the effective combat of cavities and periodontal disease.



RNomics Group

Contact

Dr. Antje Kretzschmar
 Phone: +49 (0) 341/355 36-5206
 antje.kretzschmar@izi.fraunhofer.de

Dr. Jörg Hackermüller
 Phone: +49 (0) 341/355 36-5205
 joerg.hackermueller@izi.fraunhofer.de

Competencies

- microRNA and ncRNA transcriptomics
- molecular and cell biology of ncRNAs
- bioinformatics
- microarray technologies
- chromatin-immunoprecipitation-on-chip

A range of products and services of this group can be found on page 28-29.

Profile

The RNomics Group identifies and characterizes disease-associated non-protein coding RNAs (ncRNAs) for the development of novel diagnostic markers and therapeutic targets. The group develops experimental and bioinformatic methods for this task with a special focus on applicability in disease and system-independent models as well as general use.

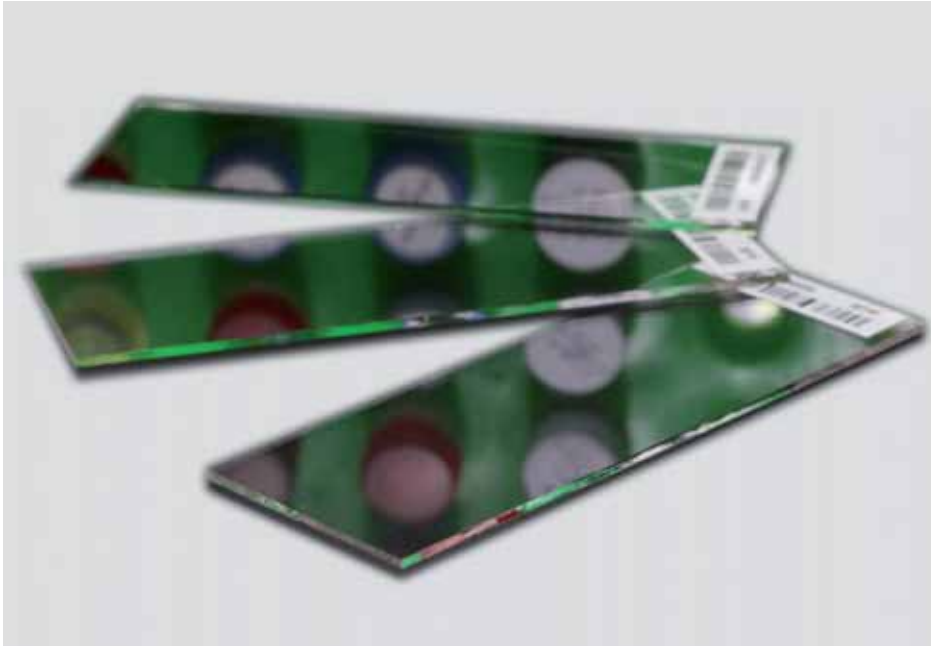
Project: Non-protein Coding RNA – a Novel Class of Biomarkers and Candidate Drug Targets

Background

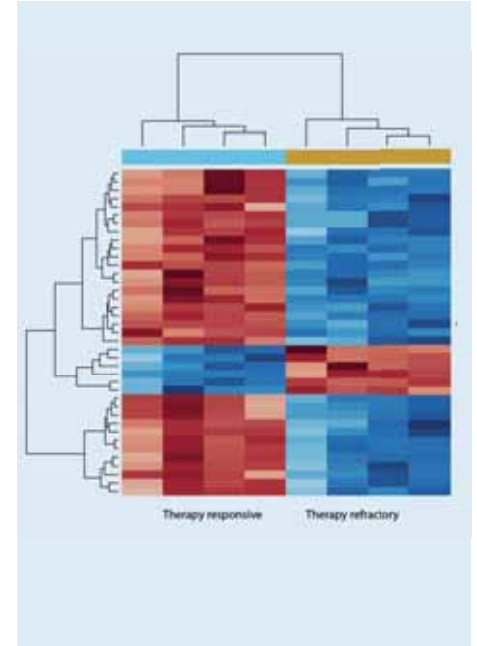
Oncologic and chronic inflammatory diseases are major drivers of health care costs in an aging society. Early diagnosis and personalized medicine are two strategies that promise reduction of costs, a growing market and benefits for patients. Both strategies heavily rely on biomarkers and many efforts show that the major hurdle for both strategies is the identification and validation of suitable markers. Just as relevant is the

development of new therapeutic strategies for both types of diseases. For example, today no curative therapy for advanced stages of prostate carcinoma, which shows a strongly age dependent incidence, exists.

Our innovative approach to this challenge is to include the alleged junk part, the bulk (98 percent) of the human genome into systematic studies for the identification of novel biomarkers, as well as therapeutic targets.



The nONCOchip™ – efficient and effective development of ncRNA biomarkers for oncological applications.



nONCOchip™ ncRNAs are able to distinguish between different stages of tumors.

Present processes for the development of biomarkers and therapeutic targets focus nearly exclusively on proteins and protein-coding RNA, as well as on biomarkers of genetic variations in the corresponding genome regions (2 percent). Thus, a fundamental source of information is ignored, because non-protein coding regions in the genome are actively transcribed into RNA. Those ncRNAs represent excellent biomarker candidates as their regulation of expression is on average more specific than those of coding RNAs and they are only marginally covered by patents. An increasing number of ncRNAs have been described to have a causal role in pathogenesis which therefore represents an new open avenue for therapeutic interventions.

Aims

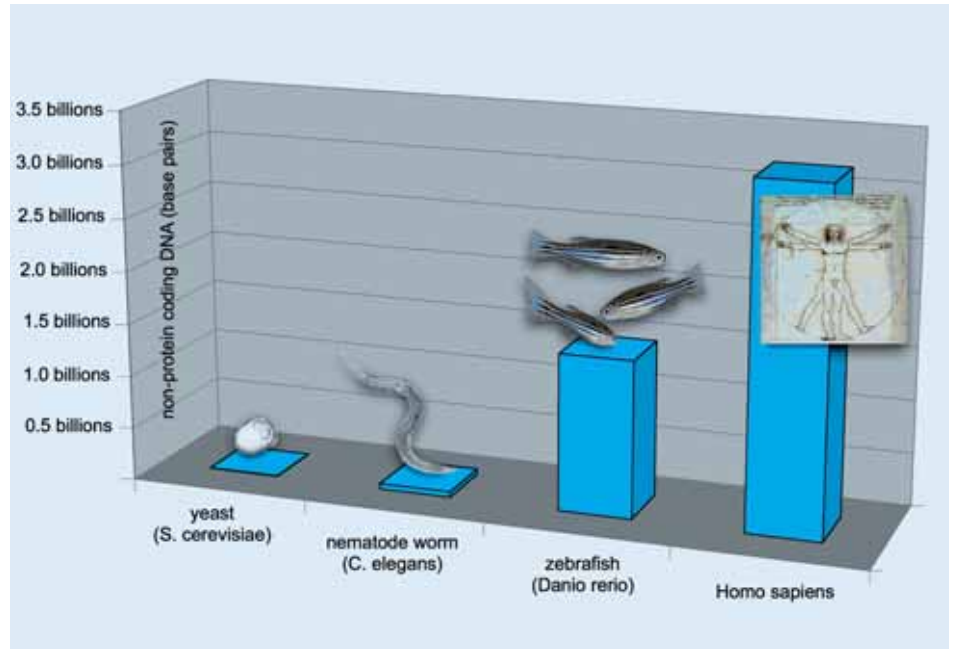
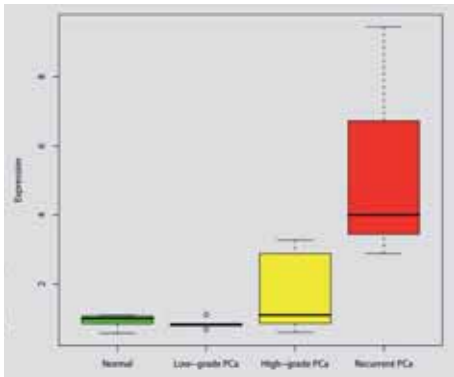
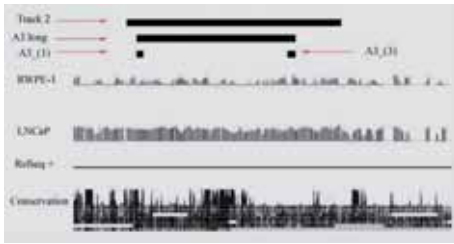
The bulk of the human genome is transcribed into RNA, but most of the ncRNAs have not yet been characterized. The ENCODE project (ENCODE Project Consortium, Nature 2007) and follow-up projects have with participation of the RNomics group demonstrated that tiling arrays and ultra-high throughput sequencing are suitable tools for the identification of novel transcripts. For larger studies, as e.g. required for the development of biomarkers, those techniques are however too material- and cost intensive. Thus, to exploit ncRNAs for biomedical applications, efficient and effective techniques for their quantification must be developed.

For the establishment of ncRNA as a therapeutic target, a high incidence disease, prostate carcinoma has been chosen as a model system. For hormone-independent, metastases-

forming stages of this disease, no curative therapies currently exist. We initially focused on a small subgroup of ncRNAs, the so called miRNAs, whose mode of action has been intensively studied. Our aim was the identification of miRNAs which are differentially expressed between tumor and healthy tissue and have influence on growth or programmed cell death of tumor cells.

Results

With the nONCOchip™ a tool has been developed, which allows the efficient and effective identification of ncRNA biomarkers for oncologic diseases. The nONCOchip™ is based on a strategy to manipulate disease relevant signalling pathways in tumor cell lines. With the aid of genome wide techniques, e.g. tiling arrays, ncRNAs are identified, whose expression levels change upon these manipulations. These ncRNAs as well as



nONCOchip™ RNA as potential marker for metastasizing prostate carcinoma.

Genomic non-coding sequences increase with the complexity of organisms.

previously known and bioinformatically predicted ncRNAs and mRNAs have been included on the nONCOchip™, a microarray. As a proof-of-concept for the performance of the nONCOchip™, two closely related stages of an aggressive brain tumor, with extremely different prognoses, have been analyzed. With the help of the nONCOchip™, a number of ncRNAs have been identified, which allow differentiation between the two groups.

In cell culture models and clinical samples several miRNAs that are lost in the tumor, have been identified. Subsequently, proteins, which are regulated by these miRNAs, have been identified in cooperation with the proteomics department of the Helmholtz centre for environmental research. Several proteins seem to be regulated by all

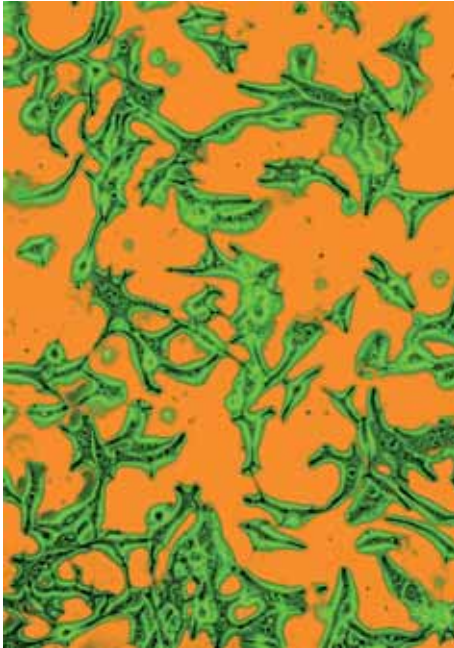
analyzed miRNAs. In addition, these proteins affect a signalling pathway, which is important for the development of prostate carcinoma. In the cell culture model, the re-introduction of the lost miRNAs into tumor cells seems to cause a slower growth and increased programmed cell death.

Potential

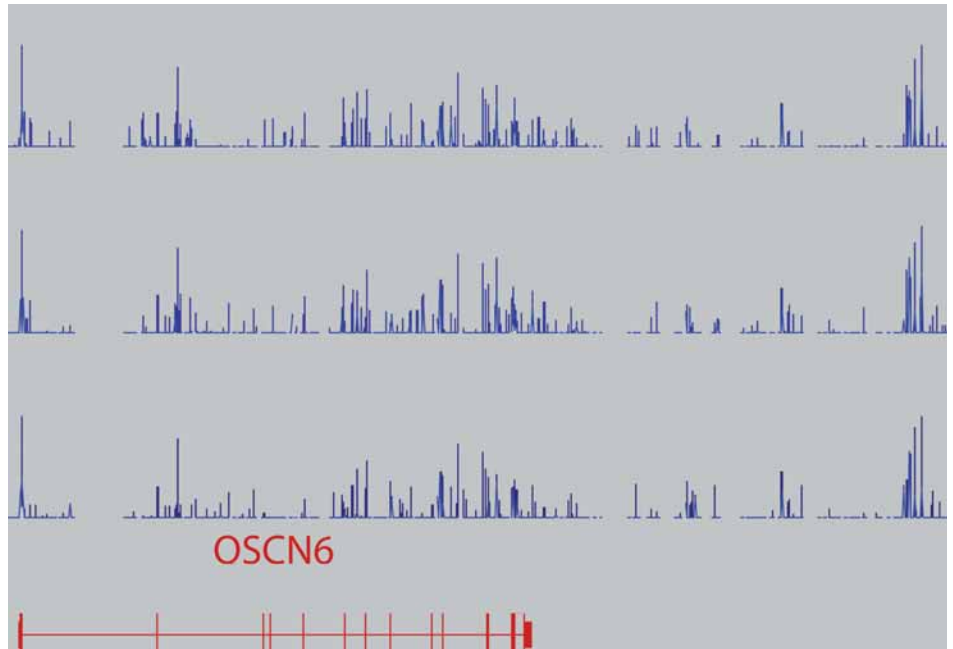
For the development of ncRNA biomarkers an essential proof-of-concept has been achieved in 2008: (i) By manipulating signalling pathways in model systems and subsequent genome-wide identification of transcripts, sets of ncRNAs feasible for biomarker development can be generated. (ii) With the aid of the nONCOchip™, which

is based on those ncRNAs, biomarker candidates can be identified, that allow the differentiation between pragmatically relevant stages of a tumor disease. In cooperation with various partners in industry and clinics, ncRNA biomarkers for difficult diagnostic and prognostic questions in oncology will be developed using the nONCOchip™. Additionally, by investigation of further signalling pathways, the application spectrum of the nONCOchip™ shall be extended and a possible transfer of the concept to other groups of diseases are to be considered.

In prostate carcinoma several candidates for therapeutic ncRNA targets could be identified that seem to be involved in a common mechanism and which seem to have a powerful impact on the growth of the tumor cells *in vitro*. The understanding of the active principle will now be extended and the feasibility as therapeutic targets will be further tested.



Morphological alteration of prostate carcinoma cells after over expression of miRNAs.



Identification of new ncRNAs by genome wide Tiling-Arrays.

The RNomics group is pursuing a platform concept for the identification of therapeutic targets as well as for the development of biomarkers based on ncRNAs. Apart from solving the exemplarily pursued question, e.g. to identify novel therapeutic targets for prostate carcinoma, the focus lies on the development of methods and strategies of general applicability. For such strategies, important proof-of-concepts have been achieved in 2008, which allows the RNomics group to offer these novel strategies to project partners or industry clients for specific application to customized questions.

Special Background

ncRNAs constitute the part of the cell's transcriptome that does not carry a signal for their translation into protein. Of the some 3.3 billion bases of the human genome, only about 1.5 percent code for proteins. Recent studies have found that the overwhelming, non-protein coding part of the genome is also transcribed with considerable activity into RNA. Expression of ncRNAs is regulated with high specificity and is associated with a remarkably large number of diseases.

This disease-relevance of ncRNAs represents a major field of research of the RNomics Group. Within international research consortia, however, the group also addresses basic questions, e. g. regarding the number and complexity of non-coding transcripts within the ENCODE consortium (ENCODE Project

Consortium, Nature, 2007; Washietl, Genome Research, 2007), the relevance of small RNAs (Kapranov, Science 2007), structured ncRNAs in model organisms (Rose, BMC Genomics, 2008), or the bioinformatic annotation of novel ncRNAs (Athanasius F Bompfünewerer Consortium, Journal of Experimental Zoology, 2007).



Molecular Diagnostic Group

Contact

Prof. Dr. med. Ulrich Sack
Phone: +49 (0) 341/97 25-506
ulrich.sack@izi.fraunhofer.de

Competencies

- genetic profiling
- cell culture techniques
- cellular function tests
- flow cytometry
- multiplex measurements of cytokines and mediators
- automated microscopy

A range of products and services of this group can be found on page 28-29.

Profile

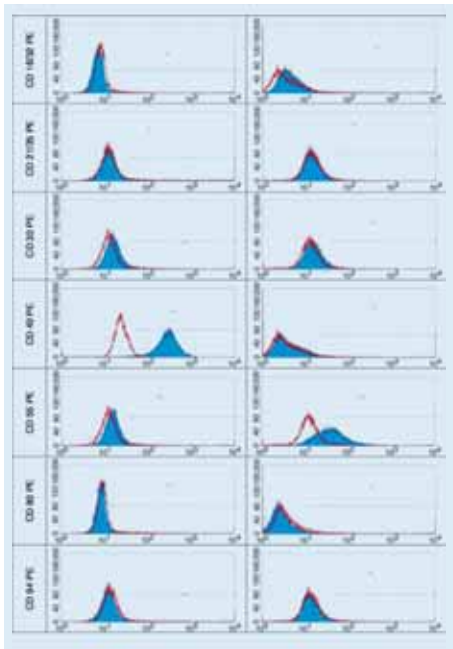
Our team develops rapid and easy-to-handle systems for the analysis and modelling of immunological and genetic processes in the fields of transplantation, inflammation research, and tumor biology. Our main foci are articular and lung diseases, which are investigated through the application of novel immunoassays, genetic analyses, complex cell culture models, and animal experiments.

Project: *In vitro* Cartilage Erosion Test

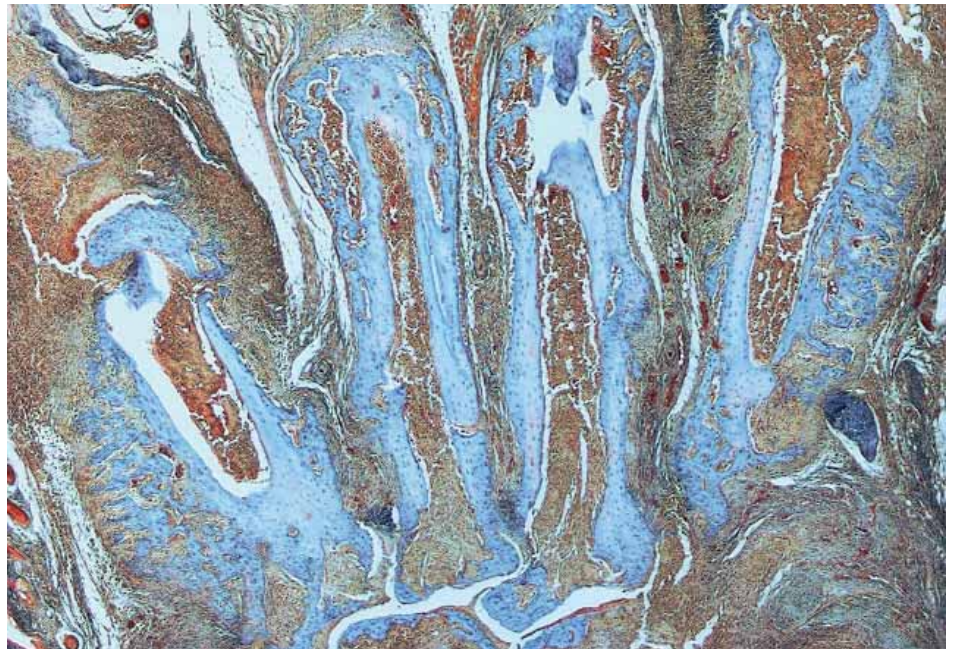
Background

Several disease modifying anti-rheumatic drugs are used today in the treatment of rheumatoid arthritis (RA). Although there are strong indicators that tumor necrosis factor (TNF) antagonists in particular can slow down progression of the actual destruction of articular cartilage, the most visible effects of this therapy are anti-inflammatory. The anti-destructive as opposed to anti-inflammatory effects

of current treatments have not yet been clarified in detail; therefore the search for such compounds has greatly intensified. Although cytokine patterns, cellular functions, and regulatory mechanisms are disturbed, it is unclear whether the disease promoting mechanism also involves immune priming or only effector functions of the inflammatory attack.



Flow cytometric comparison of invasive (left) and non-invasive (right) fibroblasts in mouse model.



Dense cellular infiltration of inflamed joints of collagen-induced arthritis of the mouse.

Aims

To investigate anti-destructive effects of novel compounds, we offer novel and commonly utilized animal models that represent various facets of RA. Standard accepted RA animal models available in our group include collagen induced arthritis, anti-collagen II antibody induced arthritis, and the new fibroblast induced arthritis model (LS48-SCID) all of which are enhanced with additional features. A novel *in vitro* approach in mice which can replace the standard model is also available. Both existing *in vitro* destruction models and the new models allow rapid assessment of pharmaceutical effectiveness and facilitate the understanding of underlying mechanisms which is a necessary requirement prior to the initiation of regulatory-determined drug development. Our *in vitro* system models the interaction between immunological and inflammatory cells with destructive fibroblasts. In this way, the effects of established as well as novel drugs in these models can be compared with particular

respect to cellular interactions. Furthermore, we aim to improve our existing model in regards to establishing a fast readout method for high throughput screening of novel anti-rheumatic and anti-inflammatory compounds.

Results

The murine system could be adapted to human conditions. This way, direct examination of antibody-based therapeutics could be carried out as expected by the commercial partners.

Potential

By investigating therapies and compounds with proposed anti-destructive potency for their effects in this model, we offer the capacity to grade the destructive potency, cytokine pattern, and cellular activation processes caused by the screened substances to find the most promising candidates in several dimensions. We propose to perform the pre-clinical study with an established anti-TNF compound, and two novel compounds: an immunosuppressive glyoxalase inhibitor (Hollenbach et al., in press), and an inhibitor of destructive enzymes based on alpha2-macroglobulin (Birkenmeier et al., 2006), which could be of interest for further investigations. Inclusion of further compounds as provided by Johnson and Johnson is intended. Finally, simplified indicators for the description of anti-destructive drugs will be established and will accelerate the search for novel compounds.



Location



Inner courtyard of the BIO CITY.



The new Fraunhofer IZI building.

BIO CITY

Funds from the Free State of Saxony and the city of Leipzig established the BIO CITY on the edge of the former convention center grounds in the south-east of Leipzig. This building complex cost 100 million euros, sits on 20,000 square meters and houses the Center for Biotechnology and Biomedicine of the University of Leipzig as well as industrial occupants; with more than 25 companies, the real estate is nearly fully occupied. Included in these companies are many cell technology enterprises such as VITA34, International AG, Haemabank AG, Curacyte AG and NeuroProgen GmbH. The building is directly across from the German National Library at the Deutsche Platz, next to the Max Planck Institute for Evolutionary Anthropology and near the institutes and clinics of the Faculty of Veterinary Medicine of the University of Leipzig. The Faculties of Medicine, Chemistry, Physics and Biology, Pharmacy and Psychology are only minutes away from the building complex of the BIO CITY. The grounds are very accessible both by public transport (tram or bus) or by car and only ten minutes from the city center. Ninety-nine

percent of the spaces in BIO CITY are rented. Many companies are attracted to the location due to its bringing together of university and industry-near research with innovative enterprises under one roof. For this reason, it is planned that the BIO CITY will extend its commercial portion in 2008-2010. This third construction period will be financed by the Free State of Saxony and the "Leipziger Gewerbehofsgesellschaft" (LGH). The new building will provide over 5,500 square meters of additional real estate for companies already present in the complex and for new occupants or spin-offs.

In this interesting scientific and entrepreneurial context, the Fraunhofer IZI has established its initial organization by renting one of the wings of the BIO CITY. Our staff make use of the conference rooms and cafeteria as well as the events organized by Bionet GmbH, which is responsible for the marketing of the BIO CITY and extending Leipzig's reputation as a significant location for health research.

The Fraunhofer IZI's new home

The accommodations in the BIO CITY represented however only a brief stop until the completion of the new institute building. The new building was constructed directly adjacent to the BIO CITY and the external façade was affixed in April 2008.

The costs for the construction of the new facilities amounted to altogether 24.6 millions Euros. 60 percent of this was financed by the European Union, and 20 percent by the Federal Ministry for Education and Research and 20 percent by the Free State Saxony. The land was made available Leipzig by the city in a (99 year) long-term lease.

After the laying of the cornerstone in September 2006 the raw building was finished in May 2007. The installation of the technical equipment and the interior fittings were completed by spring 2008. The new central building contains over 1600 m² of laboratory space and 1600 m² of office space and altogether can accommodate 200 staff members. The seven total laboratory clusters are outfitted with standard modern machinery as well as various



specialized equipment. In addition to the cell culture laboratories which all contain ultramodern bioreactors, individual units include an isotope laboratory, and GLP laboratories equipped with an emphasis on molecular-biological, proteomic, histological or immunological projects.

The design of the building represents an integrated concept – an idea is transformed into a concrete form. The architects chose as inspiration for the leitmotiv for the institute's new home the smallest basic unit of the human body – the cell. The spacious atrium, which spans the height of four floors and interconnects all levels of the house, forms the cell nucleus and is the centre of communication. With the attached modern seminar rooms the atrium stands in the centre of communicative, representative and informative meetings. Within the first months after completion of the new building the social function of the atrium was already intensively realized in its use for teaching and career development seminars, symposiums, awards ceremonies and presentations.

The cell plasma surrounds the core, with its numerous functional units of divergent tasks. The architecture translates this biological concept into a spatial concept. In addition to diversely equipped laboratory clusters the atrium is surrounded by office and business functional space. In these rooms the support functions and strategic execution of tasks occur that have been communicated through the nucleus, which ultimately represents science on the highest level. The aluminium and glass façade can also be seen as a membrane. The façade embraces the building organically; stepping away from the building allows the viewer to recognise that the façade is composed of abstracted cells.

Similarly to a cell, the Fraunhofer IZI represents a singular, contained system which is also embedded within a larger holistic federation of numerous research and education units, each of which is specialized to carry out diverse tasks and functions. On the following pages the immediate scientific environment of the Fraunhofer Institute for Cell Therapy and Immunology and the synergies developing from this field will be described.



Research Environment

Leipzig's Scientific Institutions Establish a Research Forum

In the April of 2008 representatives of the key scientific institutions in Leipzig met in order to create the "Leipzig Research Forum". The tasks and goals of the forum are to promote and coordinate long-term co-operation between University and external non-university research institutions. The central focus of the forum is to address issues surrounding cooperative research and the support of graduate students. The city of Leipzig through these measures is enhancing its status as a scientifically-attractive global higher-education location for international students.

Members from the academic arena include the Universität Leipzig, Leipzig University of Applied Sciences (HTWK) and the Leipzig Graduate School of Management (HHL). Non-university institutes include the Fraunhofer IZI, the Helmholtz-Centre for Environmental Research-UFZ, the three Max-Planck Institutes, one for Cognition and Neurosciences, one for Mathematics and one for Evolutionary Anthropology, the Leibniz Institute for Surface Modification as well Regional Geography. The Saxony Academy of Sciences and the city Leipzig are also involved in the forum.

1 Translational Centre for Regenerative Medicine (TRM)

In 2006, the Translational Centre for Regenerative Medicine was founded in Leipzig and installed in immediate proximity to the BIO CITY and Fraunhofer IZI. The TRM is a part of the excellence grants from the Federal Ministry of Education and Research and the Free State of Saxony. Institutes from across five faculties are integrated into the TRM which is directed by Prof. Emmrich. Together they established four research areas: Tissue Engineering and Materials Science (TEMAT), Cell Therapies for Repair and Replacement (CELLT), Regulatory Molecules and Delivery Systems (REMOD) and Imaging, Modelling, and Monitoring of Regeneration (IMONIT). Conceptual, preclinical and clinical research projects are supported by the TRM. The initial grant for the institution is 20 million euros over four years. The Free State of Saxony is providing an additional 17 million euros for building renovations and basic equipment. As well as playing a key role in the application to establish TRM, Fraunhofer IZI also maintains diverse links with the TRM.

2 Interdisciplinary Centre for Clinical Research (IZKF)

The Interdisciplinary Centre for Clinical Research Leipzig was founded in 1996 as a center of excellence of the Federal Ministry of Education and Research at the Faculty of Medicine to initially focus on cell-cell and cell-matrix interactions of diagnostic and therapeutic significance. Scientific focuses are on immunology, endocrinology, neurosciences and oncology. The centre also maintains various junior groups and the service units specializing in DNA sequencing and peptide technology.

3 Center for Biotechnology and Biomedicine (BBZ)

In the framework of the Biotechnology Initiative of the Free State of Saxony, five faculties joined together to create a key project to be established in the BIO CITY Leipzig: thus the Center for Biotechnology and Biomedicine was founded. The Free State of Saxony granted 200 million euros to establish the BIO CITY, including the BBZ. Particular support for Fraunhofer IZI is expected from the BBZ Members in the areas of Cell Techniques and Applied Stem Cell Biology, Bio-process Technology, Protein Structure Analysis, Mass Spectroscopy, Molecular Cell Therapy and Molecular Pathogenesis.

Clinical Competence – Transplantation

Leipzig's clinical profile is characterized by particular expertise in the fields of cell and tissue transplantation. For example, heart and lung transplants are carried out at the Heart Centre Leipzig, while the University Hospital specializes in liver, kidney and pancreas transplants. In addition, the José Carreras Foundation has opened a bone marrow transplant center, while the German Organ Donation Foundation (DSO) has set up a logistics center for tissue conservation.

4 University Hospital

The University Hospital is associated with one of the oldest medical training locations in Germany. Research focuses of the hospital include neurodegenerative diseases such as Alzheimer's disease, Parkinson's and retinal degeneration, immunological questions on immune reactivity, immunological tolerance as well as projects in molecular oncology.

5 Heart Centre

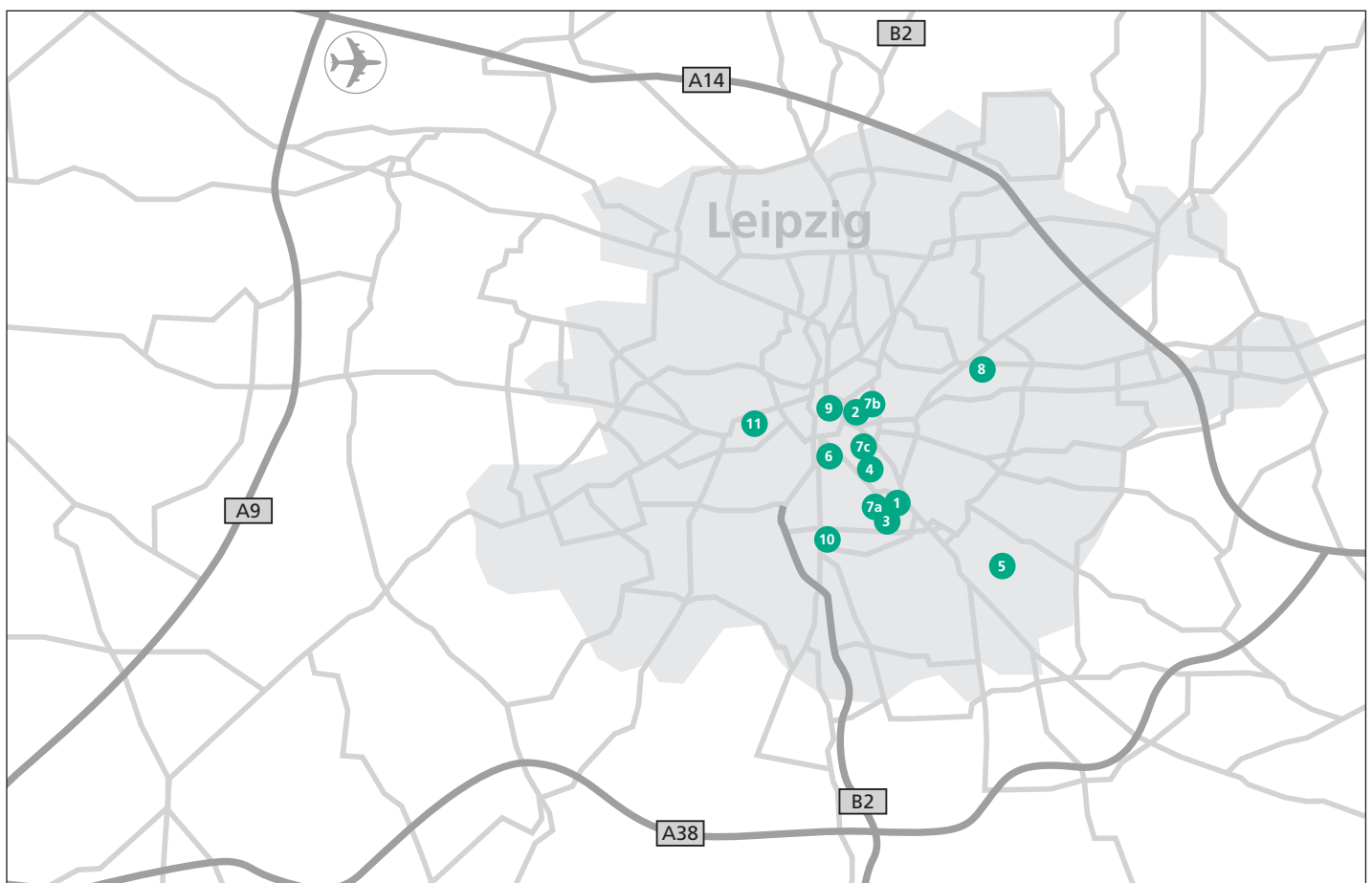
The Heart Centre Leipzig GmbH – University Hospital is a specialty hospital that houses cardiac surgery, internal medicine, cardiology, pediatrics and child cardiology. With 330 beds and 10 day-clinic places, the Heart Centre provides top-notch medical treatment for all aspects of the heart. In addition to the clinical resources, research is a major activity at the Heart Centre, in particular in the areas of developing new operative techniques and cardiovascular basic research.

6 Coordination Center for Clinical Trials (KKSL)

Innovative structures for clinical research (i. e. planning and performing clinical trials) have become very successfully established in Leipzig. The Federal Ministry of Education and Research provided funding for the Coordination Center for Clinical Trials Leipzig (KKSL) where trial assistants and doctors can be trained and clinical studies devised. In addition, Innomed Leipzig GmbH's Center for Therapy Studies (ZET) is an organization that carries out clinical trials with doctors treating outpatients. Both institutions already work very closely with Fraunhofer IZI.

6 Interdisciplinary Center for Bioinformatics (IZBI)

Thanks to financial support from the German Research Foundation (DFG), Leipzig has established an Interdisciplinary Center for Bioinformatics (IZBI). Its main tasks are the modelling of mechanisms of cellular signal transduction and data processing for cell analysis techniques. In particular, Fraunhofer IZI's RNomics Group cooperates intensively with IZBI.



Translational Center for Regenerative Medicine (1), Interdisciplinary Center for Clinical Research (2), Fraunhofer Institute for Cell Therapy and Immunology (3), Centre for Biotechnology and Biomedicine (3), University Hospital (4), Heart Center (5), Coordination Center for Clinical Trials (6), Interdisciplinary Center for Bioinformatics (6), Interdisciplinary Transgenesis Center (3), Max Planck Institute for Evolutionary Anthropology (7a), Max Planck Institute for Mathematics in the Sciences (7b), Max Planck Institut for Cognitive and Brain Sciences (7c), Center for Environmental Research (8), Leibniz Institute of Surface Modification (8), Association for the Advancement of the Health Economics of the Region Leipzig (3), University of Leipzig (9), University of Applied Science (10), Graduate School of Management (11)

3 Interdisciplinary Transgenesis Center

The Faculty of Veterinary Medicine, Faculty of Medicine and the Max Planck Institute for Evolutionary Anthropology joined forces to found a transgenesis center where pioneering techniques for the introduction and elimination of genes can be developed – for instance in connection with the development of new pathogenetic models in animals.

7a 7b 7c Max Planck Institutes (MPIs)

Cooperation with the three Max Planck Institutes in Leipzig is only natural. The Max Planck Institute for Human Cognitive and Brain Sciences (7c) provides special expertise for modern imaging technologies and very valuable facilities are accessible, such as, for example, MRI. The MPI for Mathematics in the Sciences (7b) is the sponsor of the IZBI, in addition to the university. The cooperation between the MPI for Evolutionary Anthropology (MPI-EVA) (7a) (Prof. S. Pääbo) is especially interesting and has yielded internationally recognized research in molecular and developmental biology.

8 Centre for Environmental Research (UFZ)

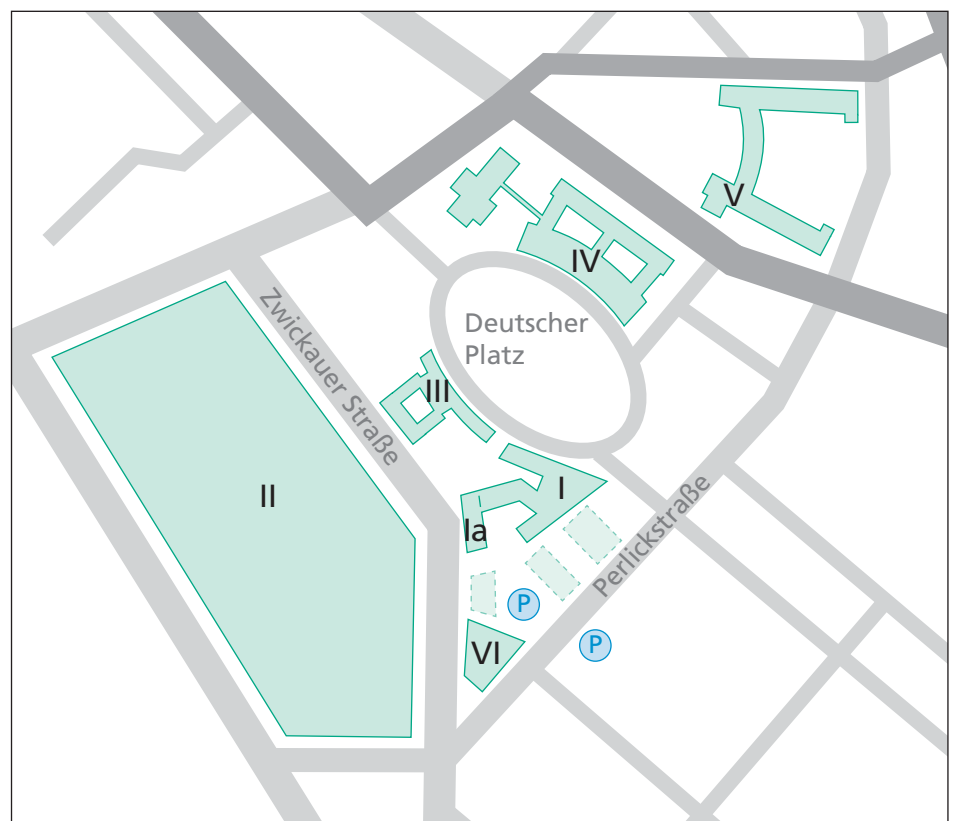
The Centre for Environmental Research (UFZ) Leipzig-Halle is a member of the Helmholtz-Gesellschaft and one of the German government's biggest research institutions. Many working groups there represent great technological experience with bioreactors for microbiology, sensor technology and cell culture.

8 Leibniz Institute for Surface Modification (IOM)

The IOM carries out application oriented basic research with the goal of transferring their results into new technologies. Their focus is on examining the interactions between radiation and materials. Knowledge of physical and chemical processes support the development and production of insulating, metallic, semiconducting and polymer surfaces.

3 Association for the Advancement of the Health Economics of the Region Leipzig (VGF)

This association, founded in 2004, has the mission to promote the region of Leipzig as a leading center for medical science and practice in Germany and internationally. The group is composed of researchers, doctors, clinics, practices, laboratories and commercial partners. Contacts in the VGF are primarily scientists, industry members, interest groups, doctors, patients and the interested public.



BIO CITY (I) with hired Fraunhofer IZI area (Ia), Faculty of Veterinary Medicine, institutes and hospitals (II), Max Planck Institute for Evolutionary Anthropology (III), German National Library (IV), Translational Centre for Regenerative Medicine (V), new building of Fraunhofer IZI (VI).

Educational Environment

Renowned higher education institutions such as the University of Leipzig, the Leipzig University of Applied Sciences (HTWK) and the private Graduate School of Management (HHL), which was re-founded after the unification of Germany, have a significant impact on the region's workforce. They are the basis for the high level of education and training one finds in the population: 14 percent are engineers or technicians and 16 percent hold a higher degree. This sets a great stage to recruit a well-trained staff.

9 University of Leipzig

The University of Leipzig was founded in 1409 and is one of the most traditional academic research institutions in Germany. Over 30,000 students are matriculated in Leipzig. In 2009, the university will celebrate its 600th anniversary with the opening of a massive new building complex that contains an Auditorium Maximum in the city center. The University of Leipzig has a strong partner in the Fraunhofer IZI for research cooperations as well as the expansion of our common teaching and professional development offerings. These contribute to raising the attractiveness of the city. Also of particular interest is the connection to veterinary medicine as there are only five faculties

for this field in Germany. For the mostly biological or medical research topics of Fraunhofer IZI, the direct contact to veterinary medicine with its many analogies to human medicine is a meaningful advantage for future developments.

10 Leipzig University of Applied Sciences (HTWK)

The Leipzig University of Applied Sciences dates back to 1764. As the largest institution of its kind in Saxony, it currently has more than 6000 students on 30 courses in the fields of engineering, economics, media and information science, computer science, mathematics and science.

11 Graduate School of Management (HHL)

The private Graduate School of Management (HHL) has proven to be an outstanding cooperation partner. A number of projects have been conducted in which medics and scientists have teamed up with business management students and junior lecturers to compile business plans and marketing strategies.





Cooperation

Research Partners

Arizona State University, Department of Chemistry and Biochemistry, USA	Helmholtz Centre for Environmental Research UFZ, Department of Environmental Immunology, Leipzig
CAS-MPG Partner Institute for Computational Biology, Shanghai, China	Helmholtz Centre for Environmental Research UFZ, Department of Environmental Microbiology, Leipzig
Center of Molecular & Macromolecular Studies, Engineering of Polymeric Materials, Lodz, Poland	Helmholtz Centre for Environmental Research UFZ, Department of Proteomics, Leipzig
Charité Campus Benjamin Franklin, Berlin	Justus Liebig University Gießen, Faculty of Medicine, Gießen
Charité Campus Mitte, Berlin	Ludwig-Maximilians-University Munich, Department Biology II, Munich
Dresden University of Technology, Faculty of Medicine, Dresden	Ludwig-Maximilians-University Munich, Faculty of Veterinary Medicine, Munich
Dresden University of Technology, Faculty of Natural Sciences, Dresden	Martin Luther University Halle-Wittenberg, Faculty of Pharmaceutical Chemistry and Bioanalytics, Halle
Ernst Moritz Arndt University Greifswald, Faculty of Medicine, Greifswald	Massachusetts Institute of Technology, Cambridge, MA, USA
Fraunhofer IAP, Polymer Nano Particles, Potsdam/Golm	Max Planck Institute for Evolutionary Anthropology, Department of Evolutionary Genetics, Leipzig
Freie Universität Berlin, Faculty for Veterinary Medicine, Berlin	Max Planck Institute for Infection Biology, RNA Biology, Berlin
Goethe University of Frankfurt am Main, University Hospital, Frankfurt/Main	Municipal Hospital St. Georg, Leipzig
Hanover Medical School, Hanover	National Cancer Institute at Frederick, HIV Drug Resistance Program, Frederick, USA
Hebrew University Jerusalem, Faculty for Medicine, Jerusalem, Israel	National Institutes of Health, Center for Cancer Research, Bethesda, USA
	National Institute on Aging, National Institutes of Health, Baltimore, MD, USA

Pompeu Fabra University, Complex Systems Lab, Barcelona, Spain	University of Leipzig, Faculty of Medicine, Leipzig	University of Sheffield, Faculty for Medicine, Sheffield, UK
Radboud University Nijmegen Medical Centre, Experimental Urology, Nijmegen, the Netherlands	University of Leipzig, Faculty of Veterinary Medicine, Leipzig	University of Stockholm, Faculty for Medicine, Stockholm, Sweden
Saarland University, Faculty for Dental Medicine, Homburg/Saar	University of Leipzig, Hospital for Radiation Therapy and Radiooncology, Leipzig	University of Torino, Department of Pathology, Torino, Italy
St. Elisabeth Hospital, Leipzig	University of Leipzig, Institute of Clinical Immunology and Transfusion Medicine (IKIT), Leipzig	University of Vienna, Department for Microbiology and Immunobiology, Vienna, Austria
Stanford University, Medical School, Stanford, CA, USA	University of Leipzig, Institute of Medical Microbiology, Leipzig	University of Zurich, VetSuisse Faculty, Zurich, Switzerland
University Hospital Rechts der Isar, Neurologic University Hospital, Munich	University of Leipzig, Institute of Organic Chemistry, Leipzig	Weizmann Institute of Science, Department of Molecular Genetics, Rehovot, Isreal
University of Buenos Aires, Institute of Pathology, Buenos Aires City, Argentina	University of Leipzig, Institute of Virology, Leipzig	
University of Copenhagen, Division of Genetics and Bioinformatics, Copenhagen, Denmark	University of Leipzig, Medical-Experimental Centre (MEZ), Leipzig	
University of Gondar, Faculty of Medicine, Gondar, Ethiopia	University of Leipzig, Translational Centre for Regenerative Medicine (TRM), Leipzig	
University of Hamburg, Center for Bioinformatics, Hamburg	University of Michigan, Department of Microbiology and Immunology, Michigan, USA	
University of Hohenheim, Faculty for Nutrition Sciences, Hohenheim	University of Münster, Faculty for Medicine, Münster	
University of Leipzig, Centre of Biotechnology and Biomedicine (BBZ), Leipzig	University of Queensland, Institute for Molecular Bioscience, St Lucia, Brisbane, Australia	
University of Leipzig, Department of Plant Physiology, Leipzig	University of Rostock, Faculty for Medicine, Rostock	
University of Leipzig, Faculty of Biosciences, Pharmacy and Psychology, Leipzig	University of Salzburg, Faculty for Biosciences, Salzburg, Austria	
University of Leipzig, Faculty of Mathematics and Informatics, Leipzig		

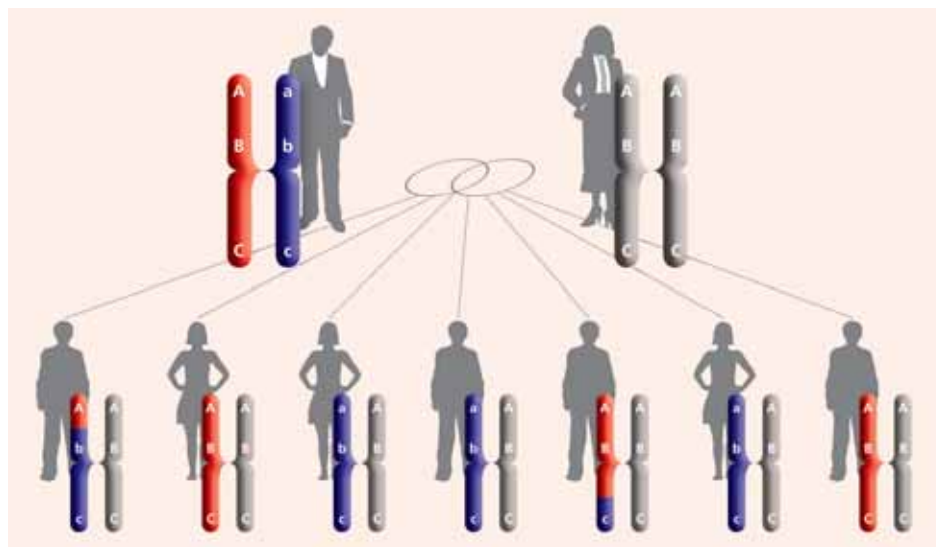
Research Cooperations

Dyslexia

Over 4 percent of all German students suffer from dyslexia, a reading and writing disorder, which causes considerable scholastic problems as well as professional problems later in life. The genetic contribution to this disorder is estimated at about 60 percent.

The Dyslexia Working Group of the Fraunhofer IZI in collaboration with the University of Jena and the TRM Leipzig pursues the goal of unearthing the genetic basis of dyslexia. Genes that are involved in the disorder will be identified and their effects on brain development will be investigated.

One of the central problems in dyslexia is the late diagnosis, as the disorder is normally only diagnosed when the child begins to learn to read and write. At this time in child development however, a significant measure of language development has already occurred, which makes intervention problematic. Fraunhofer IZI has set a long-term goal to create a diagnostic test for dyslexia on genetic basis, which would make a much earlier identification of the disorder possible. This would make timely intervention possible which could minimize later problems of the children in both schooling and career development.



Genetic variations – a possible approach for the diagnosis of dyslexia.

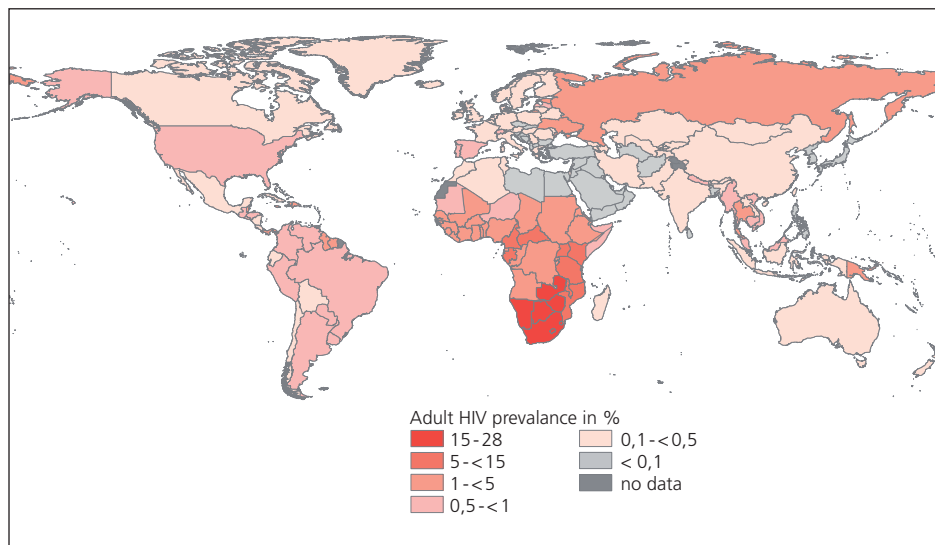
Antibody-Chimeras

The rejection of transplanted organs is one of the biggest problems in transplantation medicine. One branch of regenerative medicine focuses on measures that partially prevent life-threatening reactions of the immune system.

With this project, Fraunhofer IZI, ANTITOPE, an English company, and the University of Leipzig aim to develop a tolerance-inducing antibody to treat Graft-versus-Host-Disease. With this goal, a murine antibody has already been developed that has achieved promising results in the model system. The next step is to develop a chimeric antibody whose constant regions are of human and variable regions are of murine origin. Furthermore, a production cell line is being developed, for a large-volume production of the immunologically optimized antibody.

Ethiopia

Worldwide about 33 million people live with HIV (UNAIDS Report 2008). The largest proportion of infected individuals lives in sub-Saharan Africa. In Ethiopia, more than 3.5 percent of the population is infected with HIV. In rural areas, the HIV infection rate is above 25 percent, the unreported cases are higher. The co-infection rate of HIV with other pathogens (i.e. Plasmodium, Hepatitis C Virus, Leishmania) is unclear in Ethiopia and of a growing problem. Fraunhofer IZI, in cooperation with local Ethiopian university partners, is building a reference bank in various regions of Ethiopia to advance the study of locally present resistances as well as co-infections. The Virus-Host-Interaction Group headed by Dr. Baumann and Dr. Breun initiated the Gondar-IZI Molecular Biology Laboratory which examines blood samples collected in Ethiopia by our partners for HIV-subtypes and resistance development in cooperation with Prof. Dr. Dieter Reißig. In a field study by the Molecular Diagnostic Group, the correlation of subtype and resistance with the T-cell number is being examined. The goal of the project is to adapt and thereby



International comparison: percentage of HIV-infected persons and AIDS patients of the population, 2008. Data source: UNAIDS.

improve the care of patients in the region in cooperation with the treating physicians.

ENCODE

It is a fact that of the 3.3 billion base pairs of human DNA only about 1.5 percent code for proteins and therefore contribute to the basic construction of all human cells. The rest of the genome – approximately 3.25 billion base pairs – has been viewed up until now as genetic rubbish without any function worth mentioning.

In September 2003, the US American National Human Genome Institute founded a consortium with the goal of identifying all functional elements of the human genome sequence. The so-called ENCODE (**ENC**yclopedia **Of** **DNA** **E**lements) consortium is comprised of many international working groups and it includes Fraunhofer IZI's RNomics Group together with the University of Leipzig as the only German partner.

The international ENCODE research team succeeded recently in discovering that the segments of the genome that are termed "genetic rubbish" or non-coding genes are nearly entirely transcribed into RNA. Furthermore, these ncRNAs regulate the genes whose plan stipulates how proteins are constructed. If these processes malfunction, an imbalance in the cells can arise that may result in disease. These results present many new possibilities for diagnostics and will very surely be of therapeutic interest, for example, for cancer or heart attacks.

In June 2007, these promising results were published in the journal, *Nature*. In addition, the Fraunhofer IZI RNomics Group participated in a press conference in Leipzig about their work as a partner in ENCODE.

Large Scale Projects

RECATABI

Regeneration of Cardiac Tissue

Myocardial infarction produces severe ischemic cardiomyopathies where the necrotic tissue is deeply affected in its function. Since existing therapies cannot prevent these symptoms, new therapeutic approaches to treat these patients are highly essential. Current treatments under development comprise cellular cardiomyoplasty where myocardial or stem cells are encapsulated in natural or artificial scaffolds and grafted onto infarcted ventricles. This approach seems to have a beneficial effect although it is not yet well developed. Most of the implanted cells died soon after the treatment resulting in a partial recovery. As a consequence full tissue function and organ regeneration is not well achieved.

IZI together with four other European partners, the Institut de Recerca de l'Hospital Santa Creu i Sant Pau (Barcelona), the Universidad Politécnica de Valencia, and the Association CARDIO-MONDE, Laboratory of Biosurgical Research (Paris) was recently awarded a 4.2Mio € grant under the European FP7 framework program, which is coordinated by the University Ramon Llull Fundació Privada in Barcelona. The goal of the RECATABI consortium is to develop a bioengineered platform consisting in obtaining pre-trained cells (multipotent stem cells or pre-cardiomyocyte biomechanically and biophysically trained) to resist their implantation into a highly stressed tissue. The cells will be implanted in a newly designed biodegradable scaffolds (constructs) that will support cell survival, proper differentiation into cardiomyocyte and early extracellular instruction. In addition, the constructs are very thin and may be applied as a cardiac patch. Furthermore, the material will induce

rapid vascularization to ensure rapid tissue remodeling (removing of necrotic tissue) and regeneration into a newly functional myocardium.

ETOX-RAB – Alternative Methods to animal Experiments

Deformities and birth defects are often caused by environmental influences, such as the consumption of medications during pregnancy, in addition to genetic mutations. Most notably, substances that damage bone lead to congenital anomalies and skeletal deformations in fetuses during pregnancy. Such substances are termed embryo- or osteotoxic.

The project ETOX-RAB aims to determine the osteotoxic potential of new active agent candidates in early phases of drug development (preclinical), in order to exclude for relevant side effects. Currently, only animal experiments are available for such osteotoxic tests. The goal of ETOX-RAB is to reduce the number of these animal experiments. The new process allows testing *in vitro*, not in an animal. With the Embryonal Stem Cell Test (EST), the inhibitive effect of an active agent on the differentiation of murine embryonal stem cells is examined. Because of their pluripotent potential, embryonal stem cells can differentiate into all three germ layers of somatic cells and are therefore a suitable model for embryology. This project, which is funded by the Federal Ministry for Education and Research, is being carried out at Fraunhofer IZI in cooperation with partners from industry, technology development and different universities.

Cell Factory

The paradigm change from symptomatic treatment of degenerative diseases to causal eradication through organic implants with the help of tissue engineering is one of the most forward-looking research fields of regenerative medicine. In addition to answering critical questions such as the direction of cell differentiation, neo-vascularization, and the construction of functional, macroscopic tissue structures, the aim is to develop a concept that meets the increasing demand for bioartificial tissues and organs.

To this end, a concept was developed by the Fraunhofer Life Sciences Alliance together with the Fraunhofer Production Alliance, in order to provide an interdisciplinary overview and working arena to integrate the progressing scientific knowledge in the field with the development of production processes. The end goal is the mass production of tissue products. In addition to Fraunhofer IZI, four other Fraunhofer institutes are cooperating on "Zellwerk".

Stem Cell Technology

The Federal Ministry of Education and Research has also funded a junior research group in stem cell technology. The main objectives of the group are to expand our knowledge of pluripotent stem cells and then develop techniques that can be transferred from the laboratory to the clinic. The results are expected to shed light on the molecular control of stem cell differentiation and cell aging and to research the potential for reprogramming somatic cell cores. Technologies are tested and developed that allow work on stem cells without the need for human ovary cells or violating German stem cell legislation. One particular goal is to develop disease-specific cell lines for pathogenesis research as well as for individual pharmacological and embryotoxicological drug testing.

Transplantation Tolerance

The Federal Ministry of Education and Research has funded a junior research group developing new strategies for the induction of specific immune tolerance in cell therapy and organ transplants. The term "immune tolerance" refers to donor-specific "non-reactivity" to foreign tissue occurring even though the defense function of the immune system to infection pathogens and malignant cells is maintained. Over the next two years, classical organ transplants will be augmented in hospitals by various cell therapy techniques. A critical issue is that a strategy is required which prevents foreign cells from being destroyed. For example, the question of immune tolerance needs to be solved in order to develop an islet cell transplant to treat Diabetes mellitus. In special animal models developed in Leipzig, human immune cells can be transferred to mice, triggering immunological defensive reactions. Systems such as these can be used to test strategies that can then be transferred to common use.



Qualification



Internal Career Development

Fraunhofer EU Network

Fraunhofer-Gesellschaft, Leipzig

GLP Training Good Laboratory Practice – GLP inquiries – Quality Assurance

isomehr, Leipzig

GMP Inspections After the New AMWHV (Webinar)

Concept Heidelberg, Leipzig

Presentation Training

WSR Seminare und Beratung Hamburg, Leipzig

Quantitative Real-Time-PCR for Beginners and Advanced Learners

Invitrogen, Leipzig

Seminar Executives

Fraunhofer-Gesellschaft Personnel Development, Leipzig

Seminar Negotiation Techniques

WSR-Seminare und Beratung Hamburg, Leipzig

Validation of Excel Spreadsheets in Consideration of the New Draft of Annex 11 (Webinar)

Concept Heidelberg, Leipzig

PhD Seminar

The staff of Fraunhofer IZI hold internal communication as a core value. This is reflected not only in common excursions and events, but also in the many scientific events held each year.

With this in mind, the doctoral candidates of the different working groups regularly present their work and progress in a seminar series. In addition to the insight into the research topics and themes as well as the activities of other groups, the seminars provide the opportunity to discuss day-to-day problems with the larger community at the institute.

Scientific Exchange

Twice a year, the institute organizes a Science Day during which all of the working groups present their most important projects and network about common challenges and problems. At the end of the winter the head of the institute, the head of the groups and the Project Service Team attend the traditional strategy meeting. In 2008 the destination and the place for the exchange of ideas for the further development of the institute was Oberwiesenthal.

Teaching Activities

Roche Diagnostics GmbH / Evonik Degussa GmbH, Frankfurt / Main
Real Time Analysis of Living Cells (S)

Roche Diagnostics GmbH / IZB mbH, Planegg / Martinsried
Real Time Analysis of Living Cells (S)

Roche Diagnostics GmbH / MPI-EVA, Leipzig
Measurement and Kinetic Analysis of Real-Time Cell Reactions (S)

Roche Diagnostics GmbH / MPI-MZG, Dresden
Measurement and Kinetic Analysis of Real-Time Cell Reactions (S)

University of Leipzig

Allergology (S)
Autoimmunity (S)
Differentiation of Heart Tissue from Stem Cells (L)
Graft-versus-Host-Disease (L)
Immunology (P/L/C/S)
Immunology for Dentists (L)
Immunology/Infectiology (L)
Clinical Immunology in Practice (L)
Clinical Training (P)
Disease Models in Biomedical Research (L)
Medical Biotechnology (L)
Molecular Diagnostic (L)
Molecular Oncology and Immunology (P)
Infectiology and Immunology (PBL)
Regenerative Medicine (L)
Tolerance Induction (L)
Transfusion Medicine (S/C)
Environmental Medicine (L)

Forest Hospital Bad Dübén

Rheuma Day 2008 (medical further education) (L)

L = Lecture or student training and teaching
S = Seminar
P = Practical training
C = Course
PBL = Problem-Based Learning

Mentoring Activities

Wilhelm-Ostwald-Gymnasium Leipzig

BELL "special mentoring activity"

External Career Development

»Is seeing believing?« (Course in Immunohistochemistry)

Society for Neuroscience, Society for Neuroscience, USA

15th Workshop »Micromethods in Protein Chemistry«

GE Healthcare, Martinsried

2nd GMP-Round Table

regional council Dresden, Dresden

4th Veterinarian Congress Leipzig

University of Leipzig, Leipzig

6th Benjamin Franklin Stem Cell Workshop

Charité, Berlin

Basic Real Time PCR

Applied Biosystems, Darmstadt

Qualified Person

Concept Heidelberg, Mannheim

Introduction in FACS Analytics

Beckmann Coulter, Krefeld

Introduction Seminar Flow Cytometer FC500

Beckman Coulter GmbH, Krefeld

Advanced Training for Medical Specialist for Internal Medicine

Physician's Practice PD Dr. Hoheisel, Leipzig

GLP Currently – Equipment and Computer Validation

Center for Advanced Technological and Environmental Training FTU, Karlsruhe

Academic Teaching Training

University of Leipzig, Leipzig

Annual Conference DGK

DGK, Mannheim

Annual Conference DPG

DPG, Cologne

Course for Clinical Investigator

IMISE, University of Leipzig, Leipzig

Course for Care and Use of Labora- tory Animals

Medical-Experimental Centre, University of Leipzig, Leipzig

LightCycler-Seminar

Roche, Mannheim

Microscopy-based Cytometry: Screening Station Scan of Olympus

3rd Fluorescence Colloquium Leipzig, Leipzig

Scientific Sessions 2008

AHA, New Orleans

Sources for Stem Cell Transplanta- tions: Think Across Borders

German Association for Regenerative Medicine, Heidelberg

SPSS-Course

IMISE, University of Leipzig, Leipzig

Radiation Protection Course

University of Applied Sciences Wiesbaden, Rüsselsheim

Transgenic Animals

Charles River, Berlin

Validation of Analytical Methods in Biotechnology

Concept Heidelberg, Heidelberg

Animal Models and Animal Testing

Berlin Compact Courses, Berlin

Workshop Decyder Software

GE Healthcare/TU Dresden, Dresden

Cell Viability, Proliferation and Toxicity Assays

PromoCell Academy, Heidelberg

Reviewer and Evaluator Activities

American Association for the Advancement of Science

Dr. Jörg Baumann
Dr. Sabine Breun

Basic Research in Cardiology

Dr. Alexander Deten

Bioinformatics

Dr. Jörg Hackermüller

Canadian Institutes of Health Research (CIHR, Leaders Opportunity Fund)

Prof. Dr. Nicole zur Nieden

Cardiovasc Research

Dr. Alexander Deten

Circulation Research

Dr. Alexander Deten

Circulation

Dr. Alexander Deten

Clinical and Experimental Immunology

Dr. Nasr Hemdan

Development, Growth & Differentiation

Prof. Dr. Nicole zur Nieden

DFG

Dr. Alexander Deten

Environmental Research

Dr. Nasr Hemdan

European Heart Journals

Dr. Alexander Deten

FEBS Letters

Prof. Dr. Nicole zur Nieden

Future Virology

Dr. Jörg Baumann

Journal of Biological Chemistry

Dr. Jörg Baumann

Journal of Inorganic Biochemistry

Dr. Nasr Hemdan

Journal of Neuroscience Research

Dr. Johannes Boltze

NIH Immunology Interest Group

Dr. Jörg Baumann
Dr. Sabine Breun

NIH Virology Interest Group

Dr. Jörg Baumann
Dr. Sabine Breun

Nucleic Acids Research

Dr. Jörg Hackermüller

Planta Medica

Dr. Alexander Deten

PLOS one

Dr. Jörg Baumann

Professional Journal "Future Drugs – Expert Reviews Vaccines"

Dr. Jörg Lehmann

Professional Journal "The Open Vaccine Journal" (Editorial Board – Nomination)

Dr. Jörg Lehmann

Professional Journal "The Open Veterinary Science Journal" (Editorial Board)

Dr. Jörg Lehmann

Professional Journal "Veterinary Immunology and Immunopathology"

Dr. Jörg Lehmann

Technical Expert for the Validation of Proposals for Subsidies at the European Research Initiative EUREKA

Dr. Gerno Schmiedeknecht

Virology

Dr. Jörg Baumann

Association Memberships

American Association for the Advancement of Science

Dr. Jörg Baumann
Dr. Sabine Breun

American Heart Association (AHA)

Dr. Alexander Deten

American Society of Hematology

Dr. Christoph Schimmelpfennig

British Society for Gerontology

Dr. Alexandra Stolzing

CellNet

Prof. Dr. zur Nieden

European Autoimmunity Standardization Initiative (EASI)

Prof. Dr. Ulrich Sack

Friends of the Faculty for Veterinary Medicine of the University of Leipzig

Dr. Jörg Lehmann

German Association of Technical Assistants in Medicine

Ulrike Ehlert

German Association of University Professors and Lecturers (DHV)

Dr. Alexander Deten

German Gerontologic and Geriatric Society

Dr. Alexandra Stolzing

German Pharmaceutic Society (DPhG)

Catharina Frey-Duisberg

German Physical Society (DPG)

Dr. Alexander Deten

German Society for Cardiology (DGK)

Dr. Alexander Deten

German Society for Gerontology

Dr. Alexandra Stolzing

German Society for Immunology (DGfI)Dr. Jörg Lehmann
Prof. Dr. Ulrich Sack
Dr. Nasr Hemdan
Dr. Stephan Fricke**German Society for Regenerative Medicine**Dr. Alexandra Stolzing
Prof. Dr. zur Nieden**Immune Diagnostics**Dr. Manja Kamprad
Prof. Dr. Ulrich Sack**Immunology Interest Group**Dr. Jörg Baumann
Dr. Sabine Breun**International Society for Herat Research (ISHR)**

Dr. Alexander Deten

International Society for Stem Cell Research

Prof. Dr. zur Nieden

International Study Group for Stem Cell Therapy (ISGSCT)

Prof. Dr. zur Nieden

Regenerate

Prof. Dr. zur Nieden

Society for Biochemistry and Molecular Biology

Florian Csintalan

Society for Clinical Chemistry and Laboratory Medicine

Prof. Dr. Ulrich Sack

Society for Cytometry

Prof. Dr. Ulrich Sack

Society for Developmental Biology

Prof. Dr. zur Nieden

Society for Laboratory Animal Science (GV-SOLAS)

Dr. Jörg Lehmann

Society for NeuroscienceDr. Johannes Boltze
Alexander Kranz
Doreen Reich
Daniel Wagner**Society for Regenerative Medicine**

Dr. Stephan Fricke

Society for the Advancement of NIH Virology Interest GroupDr. Jörg Baumann
Dr. Sabine Breun**Society for Virology**Dr. Jörg Baumann
Dr. Sabine Breun**STEPS / STAIR**Dr. Johannes Boltze
Daniel Wagner**Student Society for Stem Cell Research**

Prof. Dr. zur Nieden

The RNA SocietyDr. Antje Kretzschmar
Dr. Jörg Hackermüller**Working Group Experimental Stem Cell Transplantation**

Dr. Stephan Fricke

PrizesDr. Johannes Boltze
Group: Neurorepair
3rd Hugo Geiger Prize of the Fraunhofer-Gesellschaft for the Graduation in the Area: Experimental Cell Therapy of Stroke in the RatDr. Johannes Boltze
Group: Neurorepair
Award for 7th Leipzig Research Festival for Life Sciences for Interesting Experimental Work in the Area: Experimental Cell Therapy of Stroke in the RatProf. Dr. Nicole zur Nieden
Group: Stem Cell Technology
Dr. Johannes Boltze
Group: Neurorepair
Dr. Alexandra Stolzing
Group: Stem Cell Biology
Peoples Choice Award for "Best Described Scientific Project" at the Long Night of Sciences



Events

Opening of the New Fraunhofer IZI Building

Approximately 180 guests from the political, economic and research arenas came together at the June 27th opening ceremony of the new Fraunhofer IZI, in order to celebrate the opening the Fraunhofer "Science Cell" building together with the staff. After three years of work and research in the neighbouring BIO CITY laboratories, finally the Fraunhofer IZI can make use of its new facilities which have become necessary, since the institute has grown to 120 total co-workers since the middle of April 2007. The new building which is modelled on the shape and functionality of a cell extends over 1600m² and is equipped extensively with new laboratory and office equipment. The light-flooded atrium, which serves as meeting place and communication centre with attractive social corners, forms the cell nucleus. The architects Heinle, Wischer and Partner have created optimal conditions for innovative research in modern ambience.

The costs of the new building including original procurement of equipment amount to altogether 24.6 million Euros. This support is derived from the European Union, the Free State Saxony as well as the German Federal Ministry for Education and Research. The land was made available by the city Leipzig. High-level politicians attended the opening ceremony and congratulated both the Institute director Professor Frank Emmrich and the staff of the new Institute, noting that the establishment of the Fraunhofer IZI would greatly enrich the international scientific attractiveness of the city of Leipzig. The message of the honoured speakers was clear: The importance of Regenerative Medicine and research in the area of biotechnology is on the increase and the establishment of a Fraunhofer institute focussing on cell therapy and immunology in Leipzig offers significant potential for the city Leipzig as well as the state of Saxony. This position was

affirmed by the Minister of the state of Saxony Dr. Eva-Maria Stange, the Leipzig mayor Burkhard Jung, the head of the Executive Finance Committee of the Fraunhofer-Gesellschaft Dr. Alfred Gossner as well as the pro-rector of the University of Leipzig Professor Martin Schlegel. Wolfgang Tiefensee, the German Federal Government official responsible for the New German States and also a former mayor of the city Leipzig, stressed the connection between Science and the Economy, noting: "[through this connection] scientific results can be rapidly transferred into business-relevant inventions and applied productively." Following the official speeches and congratulations the guests were given guided tours through the laboratories of the institute as well as culinary experiments at the soup bar. With a molecular cocktail in hand, guests and co-workers gave a toast to the successful future of the new Fraunhofer IZI!



Impressions of the opening of the new Fraunhofer IZI building at June 27, 2008. Picture in the middle (f. l. t. r.): Wolfgang Tiefensee, Dr. Eva-Maria Stange, Burkhard Jung, Prof. Martin Schlegel, Dr. Alfred Gossner and Prof. Frank Emmrich. Picture at the bottom: Ensemble Amarcord.

Science Summer 2008

"Every Scientist needs mathematics, mathematics doesn't need other sciences." This quote from the famous mathematician Jakob I. Bernoulli could be named as one reason for the participation of the Fraunhofer IZI in the Science Summer 2008 in Leipzig.

The Science Summer started with the "Long Night of Sciences" on June 28th. The employees of the institute conceptualized several special events and invited the visitors to taste "science cocktails". The institute presented a relaxed lounge and cocktail bar for the public to enjoy. With cocktails such as "immuno colada" or "cryopirinha" visitors were invited to stay for a while and to look, behold and to take part in different activities. Major questions answered by the staff of Fraunhofer IZI included:

- What are stem cells and what will they be used for?
- Immune system: What are anti bodies and antigens?
- What is the function of vaccines?
- Genetic engineering: What is DNA? What is RNA?

Guided tours were given by employees in which interesting views of the clean room facility for manufacture of pharmaceutical tissue production were shown. The staff spoke about ongoing projects and why the special facility is required. Visitors could become a scientist for ten minutes in the laboratory facility and experience the daily work of the employees of the laboratory, including microscopy of cells and tissue as well as electrophoresis. The personal department staff was also hard at work during the event and gave the visitors information about jobs at the institute and advice regarding themes such as applications and choice of academic study.

A special highlight was the round table discussion with the director Frank Emmrich. After a short introduction to "Regenerative Medicine and Stem Cells" an active talk developed. Visitors asked questions and discussed their fears and hopes in regards to stem cell research. The institute closed its doors midnight and said goodbye to the last of nearly 1000 visitors.

The following week a science fair was held at the city center of Leipzig. The theme of the Fraunhofer IZI booth was "The human in numbers", in which several interesting rates, masses and quantities were presented these included:

- How many heat receptors are on our hands?
- How big is the human genome?
- What is the probability to inherit your mother's blood type?

For demonstration purposes playful activities, used by many school classes were introduced. Giant microbes had to be allocated by visitors to different diseases, the volume of blood in the human body had to be estimated and cells had to be allocated the right body parts by cell memory.



Impressions of the "Long Night of Sciences" and the "Science Summer" 2008.



3rd Fraunhofer Life Science Symposium

Stroke and cardiac infarction are the most frequent causes of death in industrialized nations. Even when acute conditions are successfully treated, patients have to live with the damaging consequences. For this reason the theme of the 3rd Fraunhofer Life Science Symposium 2008 was "Ischemia and Regeneration". "The symposium offers a professional backdrop to present and discuss new therapeutic approaches for these diseases" according to Prof. Dr. Frank Emmrich, head of the Fraunhofer IZI.

On October the 24th-25th 120 scientists, physicians and economic ambassadors came together to present and discuss new therapeutic approaches. Keynote speakers such as Prof. Dr. Gustav Steinhoff (Rostock), Dr. Brigitte Onteniente (Paris), Prof. Dr. Bodo-Eckehard Strauer (Düsseldorf), Prof. Dr. Jürgen Hescheler (Cologne), Dr. Bernd Stratmann (Bochum) and Prof. Dr. Ulrich Dirnagl (Berlin) gave interesting lectures about their work. The participants from overall 12 different nations

asked for questions such as: Could the heart regenerate? Do stem cells exist in the heart? Could bone marrow stem cells regenerate cardiac tissue? Every year about 150 000 strokes occur in Germany, do stem cells represent an opportunity for therapy? How could new approaches be transferred into clinical use?

The symposium was accompanied by a poster and an industry exhibition in the bright atrium of the institute. The integration of biotechnological and pharmaceutical companies in the scientific event has the goal of bringing scientists and industry in close contact to facilitate the transfer of research from the bench to the bedside as fast as possible. The continuance of the event will take place in the following year 2009 with the title: "4th Fraunhofer Life Science Symposium: Rapid Prototyping and Scaffolds – New Techniques for Tissue Engineering".

More information: www.fs-leipzig.com



Fraunhofer Innovation Forum "Demography and Health Resources"

On October the 23rd the Fraunhofer Innovation Forum celebrated its acclaimed premiere. In cooperation with the European Union for Vitality and Active Aging (eVAA) from Leipzig this series of events should take place annually and present different topics in health care to the public. The first event occurred under the patronage of Federal Minister Dr. Annette Schavan who gave a presentation on the topic of "Demography and Health

Resources". Top-level decision makers from science, medicine, industry, politics and education discussed demographic change and the rapid changing working and living environment. Experts presented approaches to face the challenges for the modern community. The event was rounded out by a classy dinner in the festive illuminated atrium of the Fraunhofer IZI.



Further Events

Other institutes, associations and companies were attracted by the new Fraunhofer IZI. The new and modern rooms represent an optimal location for meetings, conferences and special events. During the last quarter of the year 2008 one event was followed by the other.

One of the most important events planned by external organizations was the "Science meets Business" event held on December 4th by the Chamber of Industry and Commerce (IHK). Universities and companies had the opportunity to introduce their research

or business concept. A workshop and several lectures informed the participants about themes such as innovation through cooperation, economic conditions and more. The invited guest minister of the state Saxony Thomas Jurk discussed the economic and technology policies of the free state of Saxony. He gave an overview of the potential of the region Leipzig and how current policy could be optimally used.

Furthermore Fraunhofer researchers took a particular interest in the visit of the German academic exchange service (DAAD) delegation on December the 10th. Several scientists could present

their work to post docs and senior scientists from USA. The goal was to create a base for future cooperation and scientific transfer.

Further events in 2008 were the annual meeting of the Working Group SCHOOL-BUSINESS Saxony on November the 6th, the Fraunhofer IT meeting on November 11th - 12th and the "Forum Health Policy" meeting of the CDU on November the 17th.



Prof. Dr. Frank Emmrich and the Saxony State Minister for Economic Affairs and Labor Thomas Jurk.



Minister president of the Free State of Saxony Stanislaw Tillich in discussion with exhibitors in the atrium of the Fraunhofer IZI.



Chamber of Industry and Commerce (IHK) event "Science meets Business".

Appearances at Conventions and Conferences

1st Human and Veterinary Medicine Symposium Leipzig, Infection and Immunity: Research – Development – Application (P)

21.1.2008, Leipzig

11th German Meeting on Th1/Th2 research (V)

18. - 19.6.2008, Marburg

13th Annual Meeting of the RNA Society (P)

28.7. - 2.8.2008, Berlin

2nd Annual Meeting of GHUP (V)

1. - 4.10.2008, Graz, Austria

2nd World Immune Regulation Meeting (P)

17. - 20.3.2008, Davos, Switzerland

3. Fraunhofer Life Science Symposium (V/P)

24. - 25.10.2008, Leipzig

33rd Congress of the German Society for Rheumatology (P)

19. - 22.9.2008, Hamburg

4th Innovation Forum Multiparameter Analytics (V)

27. - 29.3.2008, Senftenberg

4th Spring School on Immunology (P)

3. - 7.3.08, Ettal

6th International Congress on Autoimmunity (V)

10. - 14.09.2008, Porto, Portugal

7th Leipzig Research Festival for Life Science 2008 (P)

12.12.2008, Leipzig

Advances in Microarray Techniques (V)

7.-8.5.2008, Barcelona, Spain

Allergological and Infectiological Questions in Practice and Clinic (V)

19.1.2008, Leipzig

Annual Meeting DPG (V)

4.3.2008, Cologne

Annual Meeting of the German Society for Veterinary Medicine (P)

25.-27.6.2008, Braunschweig

Applied Biosystems RNA world tour (V)

28.1.2008, Dresden

BioStar (V)

9.-11.10.2008, Stuttgart

BMBF Contest Biofuture (P)

28.1.2008, Berlin

Crosstalk Seminar Series – Corpus Christi College (V)

Cambridge, UK

DAAD Information Tour 2008 (V)

10.12.08, Leipzig

DGfI Annual Meeting (P)

3.-6.9.2008, Vienna, Austria

DGHO (P)

10.-14.10.2008, Vienna, Austria

DGKL Annual Meeting (P)

21.-24.09.2008, Mannheim

EASI Conference (V)

12.9.2008, Porto, Portugal

Environmental Toxicology Seminar Series – University of California (V)

Riverside, USA

Forum Bioinformatics (V)

24.10.2008, Leipzig

Futuresax (V)

15.10.2008, Dresden

Gondar University Seminar (V)

6.2009, Gondar, Ethiopia

II Sympozjum Standaryzacja W Immunologii / VI Konferencja Naukowa – Szkoleniowa (V)

27.-29.11.2998, Poznan, Poland

Informa Conference »Biobanking and Biorepositories« – Evening Seminar: Comparison of Legal and Regulatory Frameworks Around Biobanking (V)

13.-16.4.2008, Zurich, Switzerland

Meeting of the Society for Tooth, Mouth and Jawbone Medicine (V)

8.11.2008, Leipzig

microRNAs Europe 2008 Meeting (P)

2.-4.11.2008, Cambridge, UK

PulmoTension Meeting (V)

18.4.2008, Frankfurt

RNA 2008 (P)

28.7.-3.8.2008, Berlin

Seminar Series – Burnham Institute (V)

San Diego, USA

Seminar Series – Wake Forest Institute for Regenerative Medicine (V)

Winston-Salem, USA

Stem Cell Center Lunch Talks – University of California Riverside (V)

Riverside, USA

TBI Winter Seminar 2008 (V)

19.-24.2.2008, Bled, Slovenia

Technology Forum Diagnostics and Bioanalytical Devices (V)

9.-10.12.2008, Frankfurt

The 6th International Workshop »Slide-Based Cytometry« (P)

3.-5.4.2008, Leipzig

O = Oral presentation

P = Poster

S = Stand



Publications

Journal Articles

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- Goettsch W, Schubert A, Morawietz H. **Expression of human endothelin-converting enzyme isoforms: role of angiotensin II.** *Can J Physiol Pharmacol.* 2008; 86 (6): 299-309
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- Haussig S, Schubert A, Mohr FW, Dhein S. **Sub-chronic nicotine exposure induces intercellular communication failure and differential down-regulation of connexins in cultured human endothelial cells.** *Atherosclerosis.* 2008; 196 (1): 210-8
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- Rothe K, Svanidze E, Tuche S, Emmrich F, Fricke S. **In vitro expansion, detection and functional characterization of human/murine CD4+ CD25+ FoxP3+ regulatory T-lymphocytes.** 7th Leipzig Research Festival for Life Science, 2008 December 12, Leipzig, Germany
- Sack U. **Activities of the German group in the European Autoimmune Standardisation Initiative (EASI).** EASI Conference, 2008 September 12, Porto, Portugal
- Sack U. **Akkreditierung und Zertifizierung in der Durchflusszytometrie.** MTA-Weiterbildung, 2008 November 25, Leipzig, Germany
- Sack U. **Allergien-Nahrungsmittelunverträglichkeiten-Pseudoallergien. Wie aussagekräftig sind immunologische Testverfahren?** Allergologische und infektiologische Fragen in Praxis und Klinik, 2008 January 19, Leipzig, Germany
- Sack U. **Autoantibody detection by indirect immunofluorescence on HEp-2-cells.** 6th international congress on autoimmunity, 2008 September 10-14, Porto, Portugal
- Sack U. **Biologistik – neuer Wachstumskern in Leipzig.** Futuresax, 2008 October 15, Dresden, Germany
- Sack U. **CD64 expression by PMN indicates infectious complications following solid organ transplantation.** DGKL-Jahrestagung, 2008 September 21-24, Mannheim, Germany
- Sack U. **Der immunkompromittierte Patient – was der Zahnarzt wissen sollte.** Tagung der Gesellschaft für Zahn-, Mund- und Kieferheilkunde, 2008 November 8, Leipzig, Germany
- Sack U. **Detection of complications following solid organ transplantation by CD64 on PMNs.** DGfL-Jahrestagung, 2008 September 3-6, Wien, Austria
- Sack U. **Möglichkeiten und Perspektiven der Multiparameterdiagnostik.** Innovationsforum Multiparameterdiagnostik, 2008 March 27-29, Senftenberg, Germany
- Sack U. **Phenotypic characteristics of arthritic fibroblasts.** 33. Kongress der Deutschen Gesellschaft für Rheumatologie, 2008 September 19-22, Hamburg, Germany
- Sack U. **Probentransport – alles geregelt?** Arbeitstreffen IML/IZI, 2008 September 27, Leipzig, Germany
- Sack U. **Regulatory affairs and accreditation in diagnostic flow cytometry.** Il sympozjum standaryzacja w immunologii/Konferencja naukowa – Szkoleniowa, 2008 November 27-29, Poznan, Poland
- Savkovic V, Kuske B, zur Nieden NI, Ding H. **Gene activation during the early differentiation of embryonic stem cells monitored by promoter-GFP constructs.** 7th Leipzig Research Festival for Life Science, 2008 December 12, Leipzig, Germany
- Schimmelpfennig C. **Homing and Survival of Ex Vivo Expanded Donor Dendritic Cells after Allogeneic BMT.** Leipziger Workshop on Cytomics and regenerative medicine, 2008 April 05, Leipzig, Germany
- Schmidt UR, Förschler A, Kamprad M, Kranz A, Emmrich F, Wagner DC, Boltze J. **Experimental umbilical cord blood cell therapy of ischemic stroke - how much time do we have for intervention?** 3rd Fraunhofer Life Science Symposium, 2008 October 24-25, Leipzig, Germany
- Schmidt UR, Wagner DC, Förschler A, Kranz A, Kamprad M, Egger D, Emmrich F, Boltze J. **Intra venous Cell Treatment of Stroke by Human Umbilical Cord Blood Cells: Investigation of the Therapeutic Time Window.** INTR20, 2008 September 10-13, Freiburg, Germany
- Schuhmann J, Müller U, Knauer J, Straubinger RK, Blessing M. **Effects of TGF- β on TH17 cell development.** 1. Leipziger Human- und Tiermedizin-Symposium Infektion und Immunität Forschung – Entwicklung – Anwendung, 2008 January 21, Leipzig, Germany
- Schutt K, Horn F, Ullmann K, Schulz C, Stadler PF, Hackermüller J, Kretzschmar AK. **A high throughput method to detect unknown microRNA-targets.** 7th Leipzig Research Festival for Life Science, 2008 December 12, Leipzig, Germany
- Schutt K, Horn F, Ullmann K, Schulz C, Stadler PF, Hackermüller J, Kretzschmar AK. **A high throughput method to detect unknown microRNA-targets.** microRNAs Europe 2008 Meeting, 2008 November 2-4, Cambridge, UK
- Schutt K. **Analysis of microRNA-targets: bioinformatical prediction and experimental validation using differential expression of microRNAs.** TBI Winterseminar 2008, 2008 February 19-24, Bled, Slovenia
- Stolzing A, Sellers D, Llewyn O, Scutt A. **Glycated ECM Harms Mesenchymal Stem Cells in Old Age: Signaling and Structural Mechanisms.** American Aging Association, 2008 May 29-June 1, Boulder, USA
- Stolzing A. **Microglial cell therapy for neurodegenerative diseases.** 3rd Fraunhofer Life Science Symposium, 2008 October 24-25, Leipzig, Germany
- Trettner S, Seeliger A, zur Nieden NI. **Scalable Production of Uniform EBs from Embryonic Stem Cells for High-throughput Screens.** 7th Leipzig Research Festival for Life Science, 2008 December 12, Leipzig, Germany

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Establishment of an objective examination technique for diagnosis and grading of GVHD by means of fully-automated, quantitative fluorescence microscopy.
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MicroRNAs lost during prostate carcinoma pathogenesis cooperatively regulate mRNAs involved in Androgen Receptor signalling.
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Experimental cell therapy of stroke – preclinical evaluation of transplantation modalities.
XVII. European Stroke Conference, 2008 May 13-16, Nizza, France

zur Nieden NI.
Embryonic stem cells for the prediction of developmental toxicity in pharmacological screening.
4. Innovationsforum Multiparameteranalytik, 2008 March 27-29, Senftenberg, Germany

zur Nieden NI.
Bioreactor Cultures for the Large-scale Expansion and Computer-controlled Growth of ESCs – Applications in Cell Therapy and Pharmaceutical Screening. Seminar series, 2008 November, Burnham Institute, San Diego, CA, USA

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Cell fate decisions of embryonic stem cells are controlled by soluble factors and physical cues. Seminar series, 2008 February, Wake Forest Institute for Regenerative Medicine, Winston-Salem, NC, USA

zur Nieden NI.
Embryonic stem cells – a powerful tool in classifying potential developmental toxins? Environmental toxicology seminar series, 2008 December, University of California Riverside, CA, USA

zur Nieden NI.
Embryonic Stem Cells for the Treatment of Bone Diseases. Crosstalk seminar series, 2008 February, Corpus Christi College, Cambridge, UK

zur Nieden NI.
Stepwise induction of osteogenic cell fate in ESCs through modulation of Wnt/CatnB signaling. Stem Cell Center lunch talks, 2008 November, University of California Riverside, Riverside, CA, USA

Graduation

Alexander Seeliger
Stem Cell Technology Group
Charakterisierung eines automatisierten Bioreaktorsystems zur osteogenen Differenzierung von murinen embryonalen Stammzellen
Diploma thesis, University of Applied Sciences Jena

Doris Wolf
Cell Engineering/GLP Group
Charakterisierung und Phänotypisierung der murinen Stammzelllinie MuSC-E8
Bachelor thesis, Anhalt University of Applied Sciences, Köthen

Dr. med. Johannes Boltze
Neurorepair Group
Experimentelle Zelltherapie des ischämischen Schlaganfalls unter Nutzung stammzellhaltiger Populationen des humanen Nabelschnurbluts in der Ratte.
Dissertation, University of Leipzig

Dr. rer. nat. Nars Hemdan
Molecular Diagnostics Group
Immunomodulatorische Effekte der Schwermetalle unter Berücksichtigung des Th1/Th2 Gleichgewichts.
Dissertation, University of Leipzig

Katharina Schutt
RNomics Group
Entwicklung von Methoden zur Detektion, zum Nachweis und zur Validierung von miRNA-Targets.
Diploma thesis, University of Leipzig

Katja Landgraf
Immunotherapy – Oncology Group
Optimierung der ex vivo-Expansion von murinen dendritischen Zellen für den adoptiven Immuntransfer in murinen Empfängertieren
Master's thesis, University of Osnabrück

Richard Schlegel
RNomics Group
Search for novel non-codings RNAs in prostate carcinoma cells.
Bachelor thesis, Universität Rostock

Sebastian Schulz
RNomics Group
Identification of novel non-coding RNAs in prostate carcinoma cells and analysis of clinical specimen.
Bachelor thesis

Tanja Luther
Immunotherapy – Oncology Group
Optimierung der Antikörperkonzentration für die durchflusszytometrische Charakterisierung von CIK-Zellen
Bachelor thesis, Anhalt University of Applied Sciences, Köthen



Introducing the Fraunhofer- Gesellschaft

Aims and Principles

The Fraunhofer-Gesellschaft is one of Germany's big four research organizations. It is currently the largest European organization conducting applied research, the outcome of which has direct benefits for business and society. Its clients and contract partners include industrial companies, the service sector and the public sector. By developing state-of-the-art technology on behalf of its clients, the various Fraunhofer institutes help reinforce the competitive strength of the economy in their local region as well as throughout Germany and Europe. Ultimately, the Fraunhofer-Gesellschaft aims to promote the development of a society that is economically successful without losing sight of social welfare or environmental responsibility. The Fraunhofer-Gesellschaft was founded in 1949 and is a recognized nonprofit organization. Its members include prestigious companies and private patrons, who help shape Fraunhofer's research policy and strategic development. The organization was named after Joseph von Fraunhofer (1787–1826), an optician from Munich, who became a successful researcher, inventor and entrepreneur.

Structure

The Fraunhofer-Gesellschaft maintains 57 institutes with around 80 research units at more than 40 locations in Germany. The vast majority of the nearly 14,000 staff are qualified scientists and engineers. They work with an annual research budget of more than 1.4 billion euros, over 1.2 billion euros of which is generated through contract research. Roughly two thirds of the Fraunhofer-Gesellschaft's research revenue stems from industry contracts and publicly financed research. The remainder is contributed by national and regional governments, partly as a means of enabling the institutes to pursue fundamental research in areas that are first likely to become relevant to industry and society after five or ten years. Affiliated research centers and branches in Europe, the USA and Asia facilitate contact to the main regions of current and future scientific progress and economic development. As an employer, the Fraunhofer-Gesellschaft offers its staff the opportunity to develop the professional and personal skills they need to take up positions of responsibility within their institute, in other scientific domains and in business and society.

Alliances in the Fraunhofer-Gesellschaft

The Fraunhofer-Gesellschaft is divided into seven thematic groups with separate offices to coordinate their joint activities.

- information and communication technology
- microelectronics
- production
- materials and components
- life sciences
- surface technology and photonics
- defense and security

Fraunhofer Life Sciences Alliance

To strengthen the biosciences, biomedicine and biotechnology, in 2001 the Fraunhofer Life Sciences Alliance was created, it comprises Fraunhofer IBMT, Fraunhofer IGB, Fraunhofer IME, Fraunhofer ITEM, Fraunhofer IZI, and Fraunhofer IVV.

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

As far as its future development is concerned, the Fraunhofer Life Sciences Alliance focuses on four core competencies harboring excellent business prospects.

The elected spokesman of the Fraunhofer Life Sciences Alliance is Prof. Uwe Heinrich, who heads the Fraunhofer Institute for Toxicology and Experimental Medicine (Fraunhofer ITEM) in Hanover.

Fraunhofer IZI has always been a member of the Fraunhofer Life Sciences Alliance, and judging by the market experience of the various life sciences institutes, it appears unlikely that the Fraunhofer-Gesellschaft will ever be able to finance long-term, risky pharmaceutical product development under its own auspices. Therefore, the institutes in the Fraunhofer Life Sciences Alliance (including Fraunhofer IZI) concentrate on developing and offering research-intensive services. However, this does not rule out the possibility of internally financed developments being taken to an advanced level on occasion – especially in the field of new cell and tissue engineering products.

Core Competencies of the Fraunhofer Life Sciences Alliance

- accelerated drug development
- regenerative medicine
- production and safety of foods and animal feed
- biotechnical production, evaluation

Institutes in the Fraunhofer Life Sciences Alliance

Fraunhofer Institute for Biomedical Engineering (IBMT)
 Ensheimer Straße 48
 66386 St. Ingbert
 Phone: +49 (0) 6894/980-0
www.ibtm.fraunhofer.de
info@ibmt.fraunhofer.de

Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB)
 Nobelstraße 12
 70569 Stuttgart
 Phone: +49 (0) 711/970-4001
www.igb.fraunhofer.de
info@igb.fraunhofer.de

Fraunhofer Institute for Molecular Biology and Applied Ecology (IME)
 Forckenbeckstraße 6
 52074 Aachen
 Phone: +49 (0) 241/60 85-0
www.ime.fraunhofer.de
info@ime.fraunhofer.de

Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM)
 Nikolai-Fuchs-Straße 1
 Main entrance: Stadtfelddamm
 30625 Hannover
 Phone: +49 (0) 511/53 50-0
www.item.fraunhofer.de
sekretariat@item.fraunhofer.de

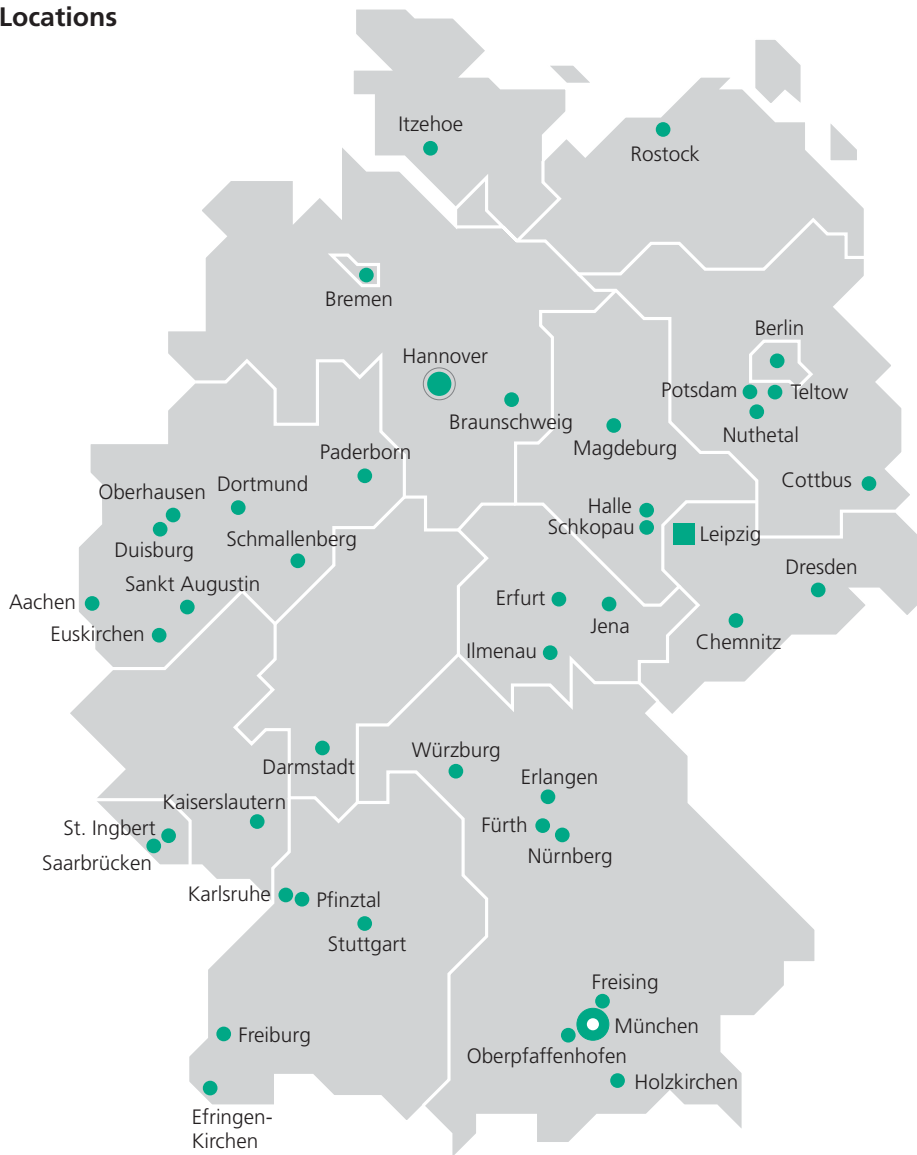
Fraunhofer Institute for Cell Therapy and Immunology (IZI)
 Perlickstraße 1
 04103 Leipzig
 Phone: +49 (0) 341/355 36-1000
www.izi.fraunhofer.de
info@izi.fraunhofer.de




Fraunhofer Institute for Process Engineering and Packaging (IVV)
 Giggenhauser Straße 35
 85354 Freising
 Phone: +49 (0) 8161/491-0
www.ivv.fraunhofer.de
info@ivv.fraunhofer.de

Head of the Fraunhofer Life Sciences Alliance

Dr. Claus-Dieter Kroggel
 Fraunhofer Institute for Toxicology and Experimental Medicine
 Nikolai-Fuchs-Str. 1
 30625 Hannover
 Phone: +49 (0) 511/53 50-103
www.lifesciences.fraunhofer.de
claus.kroggel@vls.fraunhofer.de

Locations



-  Central Office, Munich
-  Central Office of the Fraunhofer Life Sciences Alliance, Hanover
-  Fraunhofer IZI, Leipzig

Head Office

Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e. V.
 Hansastrasse 27c
 80686 München
 Phone: +49 (0) 89/12 05-0
 Fax: +49 (0) 89/12 05-7531
info@fraunhofer.de
www.fraunhofer.de

Executive Board:

Prof. Dr. Hans-Jörg Bullinger,
 President of the Fraunhofer-Gesellschaft, Corporate Management and Research

Prof. Dr. Ulrich Buller,
 Research Planning

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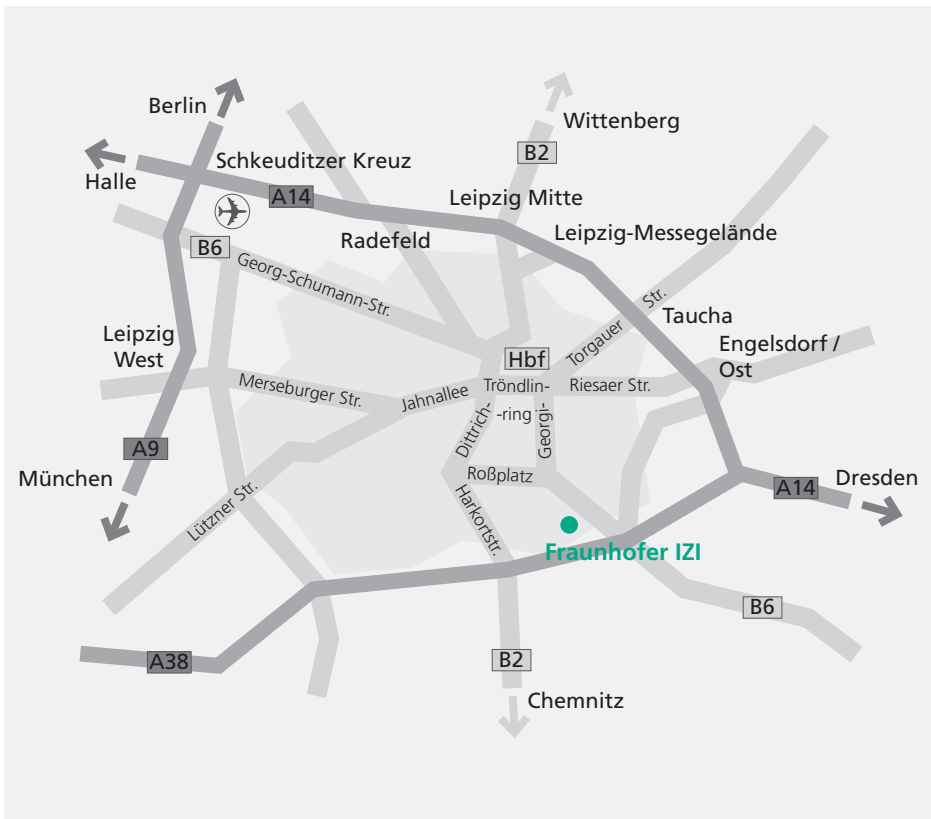
Franz Miller
 Phone: +49 (0) 89/12 05-1300
 Fax: +49 (0) 89/12 05-7513
franz.miller@zv.fraunhofer.de

Historical Fraunhofer Glasworks
 Fraunhoferstrasse 1
 83671 Benediktbeuern



Fraunhofer IZI Contact Information

Function	Contact	Phone / Email
Administration, Personnel Development, Agent for Managerial Integration Management (BEM)	Patric Nitz	Phone: +49 (0) 341/355 36-9200 patric.nitz@izi.fraunhofer.de
Biological and General Safety	Dr. Andreas Schubert	Phone: +49 (0) 341/355 36-5105 andreas.schubert@izi.fraunhofer.de
Equal Opportunities	Silvana Wiesel	Phone: +49 (0) 341 / 355 36-9201 silvana.wiesel@izi.fraunhofer.de
Equipment Management, Safety, Building Agent	Dirk Peisker	Phone: +49 (0) 341/355 36-9533 dirk.peisker@izi.fraunhofer.de
GMP Officer/Head of Production (Drugs Act)	Dr. Gerno Schmiedeknecht	Phone: +49 (0) 341/355 36-9705 gerno.schmiedeknecht@izi.fraunhofer.de
GMP Quality Assurance, Responsible Person under Drugs Act	Catharina Frey-Duisberg	Phone: +49 (0) 341/355 36-9710 catharina.frey-duisberg@izi.fraunhofer.de
Head of Institute	Prof. Dr. Frank Emmrich	Phone: +49 (0) 341/355 36-9105 frank.emmrich@izi.fraunhofer.de
Head of GLP Test Facility, Responsibility Under Section 47 (2) Infection Protection Act	Dr. Jörg Lehmann	Phone: +49 (0) 341/355 36-1205 joerg.lehmann@izi.fraunhofer.de
Head of Quality Control (Drugs Act)	Kati Kebbel	Phone: +49 (0) 341/355 36-9712 kati.kebbel@izi.fraunhofer.de
IT Speaker	Dr. Jörg Hackermüller	Phone: +49 (0) 341/355 36-5205 joerg.hackermueller@izi.fraunhofer.de
Librarian	Cornelia Gruhle	Phone: +49 (0) 341 / 355 36-9240 cornelia.gruhle@izi.fraunhofer.de
Operation Engineer	Falk Hoffmann	Phone: +49 (0) 341/355 36-9555 falk.hoffmann@izi.fraunhofer.de
Patents and Intellectual Property Rights	Ines Manleitner	Telefon: +49 (0) 341 / 97 25-807 ines.manleitner@izi.fraunhofer.de
Personnel	Ute Schmidt	Phone: +49 (0) 341/355 36-9210 ute.schmidt@izi.fraunhofer.de
Procurement, Controlling	Kristina Gentzsch	Phone: +49 (0) 341/355 36-9220 kristina.gentzsch@izi.fraunhofer.de
Project Management under Section 3 (8) Genetic Engineering Act	Dr. Sebastian Ulbert Dr. Jörg Baumann Dr. Sabine Breun	Phone: +49 (0) 341/355 36-2106 sebastian.ulbert@izi.fraunhofer.de Phone: +49 (0) 341 / 355 36-2505 joerg.baumann@izi.fraunhofer.de Phone: +49 (0) 341 / 355 36-2506 sabine.breun@izi.fraunhofer.de
Project Service, Business Development, PR	Dr. Wilhelm Gerdes	Phone: +49 (0) 341/355 36-9300 wilhem.gerdes@izi.fraunhofer.de
Radiation Protection Officer	Dr. Peter Ruschpler	Phone: +49 (0) 341 / 355 36-2605 peter.ruschpler@izi.fraunhofer.de
Responsibility under Section 47 (2) Infection Protection Act, Animal Protection Agent	Dr. Jens Knauer	Phone: +49 (0) 341/355 36-1206 jens.knauer@izi.fraunhofer.de



Fraunhofer-Institut für Zelltherapie und Immunologie
 Perlickstraße 1
 04103 Leipzig
 Germany

Reaching Fraunhofer IZI by car
A9 – exit Leipzig-West

Take the B181 heading for the city center ("Zentrum"), follow the B87 (Merseburger Straße, Lützner Str., Jahnallee). After the central railway station turn right towards Augustusplatz (Leipzig Opera House). At Augustusplatz turn left and keep to the right, afterwards follow Prager Straße. Turn right onto "Alte Messe" and after the second intersection turn right into Puschstraße. At the end of the road turn left into Perlickstraße.

A14 – exit Leipzig-Mitte

Take the B2 (via Maximilianallee) heading for the city center ("Zentrum"), follow B2 (via Gerichtsweg). Turn left onto Prager Straße (B2) heading for "Alte Messe". Then turn right onto "Alte Messe" and after the second intersection turn right into Puschstraße. At the end of the road turn left into Perlickstraße.

38 – exit Leipzig-Süd

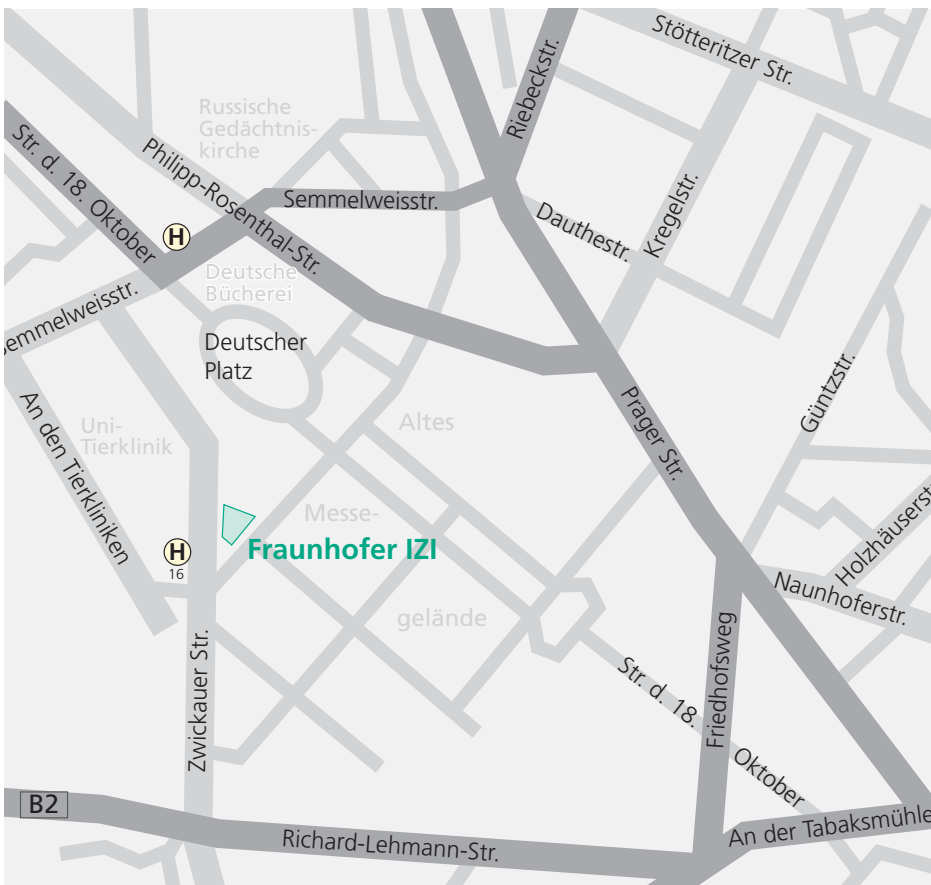
Take the B2 heading for the city center ("Zentrum"), turn off into Richard-Lehmann-Straße. Follow Richard-Lehmann-Straße and exit before the BMW car show room into Zwickauer Straße heading for "Alte Messe". Turn right onto Perlickstraße.

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Travel to Leipzig Central Station ("Leipziger Hauptbahnhof"), take the number 16 tram heading for Löbnig, get off the tram at "An den Tierkliniken".

From the airport

Take the train to Leipzig Central Station ("Leipziger Hauptbahnhof"). Then continue by tram (see above).



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Sender
Name:
Company/Institute:
Address:
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www.izi.fraunhofer.de
info@izi.fraunhofer.de
Fax: +49 (0) 341 / 355 36-9921

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Fraunhofer-Institut für Zelltherapie und Immunologie
Öffentlichkeitsarbeit
Perlickstraße 1
04103 Leipzig

Sender
Name:
Company/Institute:
Address:
Email:

www.izi.fraunhofer.de
info@izi.fraunhofer.de
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Fraunhofer-Institut für Zelltherapie und Immunologie
Öffentlichkeitsarbeit
Perlickstraße 1
04103 Leipzig

Editorial Team

Frank Emmrich
Jens Augustin
Christina Kühn

Layout & Typesetting

Michaela Grahn

Translation

Sonya Faber

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Editorial Address

Fraunhofer-Institut für Zelltherapie
und Immunologie
Perlickstraße 1
04103 Leipzig

www.izi.fraunhofer.de
wilhelm.gerdes@izi.fraunhofer.de

**Fraunhofer-Institut für Zelltherapie
und Immunologie**

Perlickstraße 1
04103 Leipzig

Phone: +49 (0) 341/355 36-1000

Fax: +49 (0) 341/355 36-9921

www.izi.fraunhofer.de

info@izi.fraunhofer.de