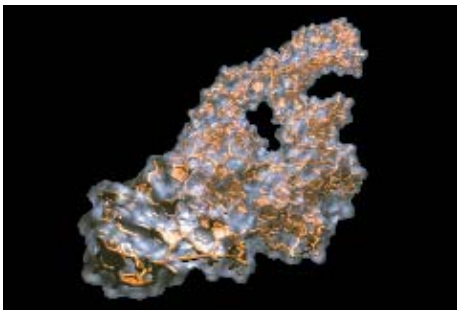
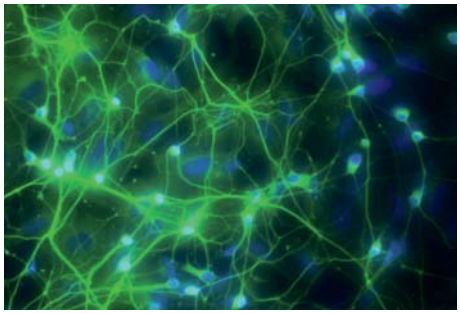
IZI

Fraunhofer Institut Zelltherapie und Immunologie

Annual Report 2005/2006

Growth and Performance





Annual Report 2005/06

Growth and Performance

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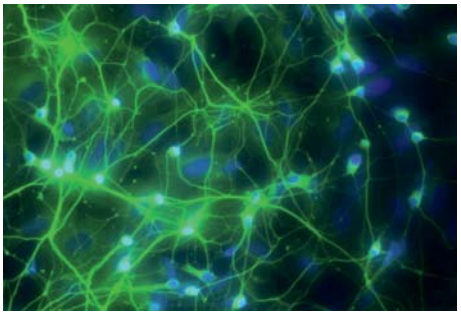
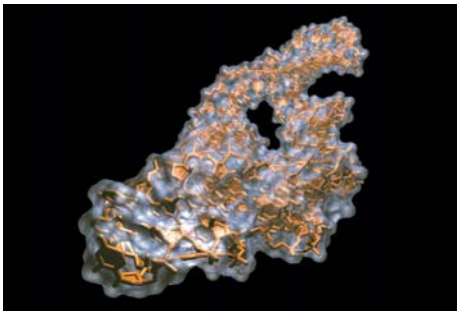
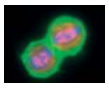


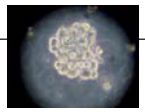


Preface

1998 

2000 

2001 Fraunhofer Verbund Life Sciences

2003 

The 29th of April 2005 was a remarkable day. Following a decision taken by all the European immunology associations, the 29 April 2005 was celebrated as European Immunology Day for the very first time. On the very same day, a particularly special 'baby' was born in Leipzig – the city's first Fraunhofer Institute. How apt that it was IZI – the Fraunhofer Institute for Cell Therapy and Immunology!

Immunology is the science of the immune system. Although comparable with the nervous system in terms of function and importance, the immune system does not have a clearly distinguishable appearance. Nevertheless, similar to the central nervous system, the immune system also has the power to recognize and process stimulatory signals, to respond to them using a variety of graded reactions, and to recall previous events – meaning it even has a certain ability to learn. During the course of evolution, the immune system has developed a unique ability to distinguish between molecules belonging to the body and foreign molecules by initially identifying both and then evaluating each one. This enables misrecognition to be avoided, which would have fatal consequences for the entire organism. Over the millions of years of evolution, the immune system has perfected itself into an efficient weapon against a constantly changing and rapidly adapting hostile environment of bacteria and viruses. However, the immune system is often overtaxed by the new methods of medical treatment which arose in the 20th century.

For example, complex operations are now possible in which cells and entire organs are transplanted from one individual to another. Unfortunately, the immune system defends itself by rejecting the donated tissue. We use the findings of modern immunology to determine the tissue types of both donor and recipient and to find the most suitable combinations. Even so, the ideal situation – i.e. no rejection whatsoever – can only be achieved with identical twins.

Consequently, our task is to teach the immune system not to reject a cell or organ transplant – without letting down its guard against pathogens (infectious germs). At present, patients undergoing organ transplants are treated with immunosuppressive drugs to subdue the immune system as a whole. The problem is that this approach raises the risk of infectious disease and may even cause the formation of malignant tumours. Therefore, a specific immunological tolerance to transplants is the central objective, and an important area of IZI's future work.

We are living in an age in which average life expectancy is still on the rise. Predictions in the 1960s that life expectancy would flatten out have proved unfounded. At present,

2004

2005

2006

no one would venture a forecast as to how old humans could actually become biologically – a blessing in some people's eyes, a curse in others'. The fact is that in recent times, the retirement years have become increasingly important, and this needs to be taken into account in many different respects.

Everyone wants to enjoy old age without becoming frail or infirm, and without becoming a burden on their family or society. As time goes on, acute diseases will give ground to chronically degenerative diseases in which organ defects and organ damage are particularly prominent. Fresh approaches need to be found to tackle this problem. Probably the most important tack is a new interdisciplinary subject which only emerged a few years ago and is becoming ever more important in international scientific development: regenerative medicine.

Regenerative medicine emerged with the discovery that local stem cell niches are to be found in all the organs examined – not just during early childhood but also in adults. These groups of cells harbour the potential for repair that can be harnessed. The associated scientific findings have led to the hope that by achieving a thorough understanding of the processes taking place, we will also be able to control them. Some researchers even believe that a fundamental paradigm change is about to occur in medicine, assuming we succeed in exploiting endogenous (i.e. the body's own) repair processes to serve medicine. This would pave the way for much gentler therapy techniques which are better suited to the biological system.

As far as new types of therapy are concerned, the most important core area is probably cell therapy. Seen in a broader sense, it covers the transplantation of cells, tissue and organs, and can even be regarded both actively and passively, i.e. as therapy using cells and on the other hand as therapy of cells with signal pathways inside the cell being influenced to control, activate and differentiate cells down a particular pathway. Cell therapy is therefore being explored by a number of groups at IZI. They investigate aspects of the isolation of stem cells from different tissues, their careful preparation, reproduction and differentiation, and also the circumstances of cells' migration through tissue, including the contacts they seek and find and the signals that attract and control them, and of course the functions they can exercise locally by repairing or replacing damaged tissue. Some of IZI's therapy techniques, such as the treatment of acute stroke, have already made substantial progress and are being prepared for clinical application in comparable large animal models.

Given the history of the Fraunhofer Society, whose development has largely been shaped by engineering and technical disciplines, and which is primarily geared to practical application and industrial cooperation, it might be queried whether a Fraunhofer Institute with a biomedical focus can successfully find its place in the research landscape – and above all generate external project funding in line with the Fraunhofer system.

We are both pleased and proud of the fact that during the years of intensive preparation and debate regarding IZI's profile, experts never doubted the need for the institute. As a result, the decision to set up IZI was approved unanimously by the Senate of the Fraunhofer Society with no abstentions. Following its first steps into practical existence in 2005 and its first full year of business in 2006, it is apparent that this confidence was justified. In addition to the interesting research projects launched by IZI and its first important findings, the number of industrial contacts, lines of negotiation and assignments in various areas of business has greatly exceeded our initial expectations.

The integration of IZI's programme into research policy and the surrounding environment also deserve special mention. The fact that Leipzig was always at the top of the list for the new institute during the intensive review of IZI's programme and discussions with experts from the Fraunhofer Society boosted our confidence no end and at the end of the day is a well-deserved compliment for Saxony's research policy and the development policy in Leipzig. The Free State of Saxony's biotechnology programme from the year 2000 paved the way for BioCity – along with a considerable scientific potential – to be established in the neighbourhood. Thanks to the intensive efforts of Mayor Tiefensee and Premier Milbradt, the foundation of IZI was mapped out in late 2004 and early 2005 with a key role being played by the German Ministry of Research and Technology. It is an important example demonstrating that in this day and age, a project of this scale can only be successfully launched if all those with political responsibility are convinced of its worth and pull together.

Accordingly, Leipzig has reached the final round of an important national research-policy competition – and the University of Leipzig can now set up a research centre for regenerative medicine whose concept superbly augments the mandate defined by IZI.

We had to begin our experimental work without having laboratories of our own. We are indebted to the invaluable personnel and structural assistance from the University of Leipzig's Institute of Clinical Immunology and Transfusion Medicine and the extraordinarily fortunate circumstances resulting from being able to rent facilities in BioCity Leipzig on Deutscher Platz in south-east Leipzig. There we encountered an environment of university institutes and departments such as the Max Planck Institute for Evolutionary Anthropology as well as more than 25 adjacent firms. Thanks to the professional approach and outstanding assistance from LGH Leipzig, the owner and operator of BioCity, who understood exactly what we needed, in connection with tremendous support from the Fraunhofer's Society's construction department, we managed to equip an entire wing of BioCity with laboratories in record time without any lost time. The fact that the clean rooms for cell engineering for the GMP-compliant production of clinical samples were planned, built and qualified in the record time of just ten months should be particularly emphasized. Furthermore, by the end of the first complete business year, IZI had already taken on a total of 71 staff, underlining just how dynamic the development of IZI has been. As the head of IZI, I would therefore like to express my thanks and appreciation to the young team responsible for launching the Fraunhofer Institute for Cell Therapy and Immunology in Leipzig so successfully.

Prof Frank Emmrich
Head of the Fraunhofer Institute for Cell Therapy and Immunology

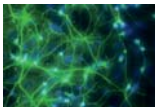
Leipzig, 1 March 2007

Profile

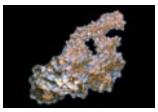
IZI's core competencies

Biotechniques – Models

Immunology – Immunomodulation



Cell Therapy – Active Agents



Molecular Biology – Individualized Medicine

Summary

The Fraunhofer Institute for Cell Therapy and Immunology complements the Fraunhofer Life Sciences Alliance by adding expertise in the fields of biotechnology, pharmacy, regenerative medicine and individualized medicine. At the forefront of its wide-ranging mandate are the current challenges of medicine in response to our ageing society, whose expectations in terms of both health and quality of life in retirement are rising fast.

In its narrow sense, cell therapy means the transfer of cells to replace lost functions and even to adopt additional active tasks. It 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 further development of immunomodulation techniques such as vaccination.

IZI serves clients from the bio-technology industry, suppliers of medical equipment and pharmaceutical companies by performing intelligent, research-intensive services and development projects. The range of services offered by IZI 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.

Examples of product developments include manufacture of ligands for cell receptors for use in pharmaceuticals, cellular materials, inhibitors, vaccines, monoclonal antibodies, diagnosis and monitoring techniques, cell lines, diverse cell and tissue specimens, and technical sensor and auxiliary systems, for instance for imaging and experimental disease models. Other services include organizing and consulting on Phase I and II clinical trials, assistance in the licensing procedures for cell and pharmaceutical products, and procuring manufacturing approval.

Outline

During an evaluation carried out in 1998, it was recommended to the Fraunhofer Society to become more involved in the life sciences. This led to the expansion of activities in this field, including the foundation of the Fraunhofer Life Sciences Alliance in 2001. In 2003 it was decided to set up another life science institute in Leipzig.

Leipzig harbours a number of advantages. These include the partnership with not only the University of Leipzig's Faculty of Medicine, which has been increasingly successful in recent years, but also the University Hospital, which is very open to scientific research. The Leipzig–Halle region contains several non-university biological and biotech research centres operating under the auspices of the Max Planck Society, the Helmholtz Society and the Leibniz Association. Under its Biotechnology Initiative, the Free State of Saxony spent half the €400 million invested throughout Saxony in 2000 to support medical biotech in Leipzig.

The concept study entitled Cell Therapy and Immunology was judged by the Senate of the Fraunhofer Society to be especially promising and practical, and was accepted for the Leipzig institute.

The proximity of BioCity combined with the prudent planning and preparation enabled a generous transition solution in which interim premises within walking distance of the departments and institutes of the Faculty of Medicine and the Faculty of Veterinary Medicine were rented and equipped.

The nucleus of IZI was formed by the Institute of Clinical Immunology and Transfusion Medicine (IKIT) and the Department of Clinical Immunology at the University of Leipzig, both headed by Prof Frank Emmrich. Some IKIT staff transferred to IZI, while others supervise projects or teams at IZI alongside their regular university work. In return, the growing potential of IZI, especially in professional project acquisition and project management, has resulted in a whole series of joint applications and successful project awards in conjunction with partners from faculties at the University of Leipzig. The award of a Translation Centre for Regenerative Medicine to the University of Leipzig made a splash throughout Germany. This project involves funding of €20 million for the next four years along with another €17.5 million for building and equipping laboratories.

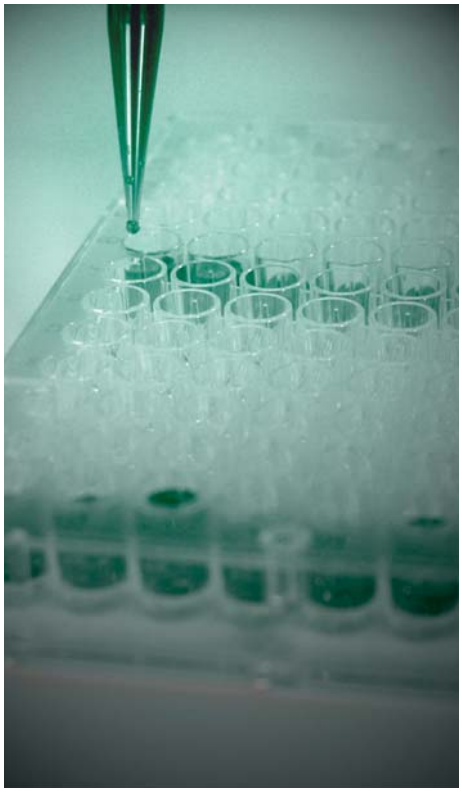
IZI was officially founded in April 2005. Its first experimental work was conducted under a cooperation agreement with the University of Leipzig at the Max Bürger Research Centre on Johannisallee, before being continued and extended at IZI's own laboratory at BioCity Leipzig in autumn 2005. This was only possible because 1,500 square metres of laboratory and office space at BioCity had been swiftly equipped thanks to smooth cooperation on the part of all those involved. In this connection 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 22 September 2006, the cornerstone for IZI was laid right next door to BioCity for a 4,000 sqm building, which when complete will contain exceptional working conditions.

In line with its core competencies, during its development phase IZI is currently divided into twelve thematically clustered groups. These groups are the primary organizational

element and are managed on the principle of business units. Every year, the group leaders negotiate the budget they require with IZI's management. The groups and the management are supported by the project service team (PST) – an organizational unit in charge of initial acquisition, project configuration (business development), market observation and public relations. The team supports the groups in applying for projects, negotiations and project management, and is also responsible for content controlling.

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 Society 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 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.

At any rate, IZI is ready and willing to provide its partners and clients with innovation and high-quality services covering the entire spectrum of the supply chain from conceptual work and laboratory trials through pre-clinical evaluation using small and large animal models to the GMP production of clinical samples – as well as the organization and supervision of clinical studies.



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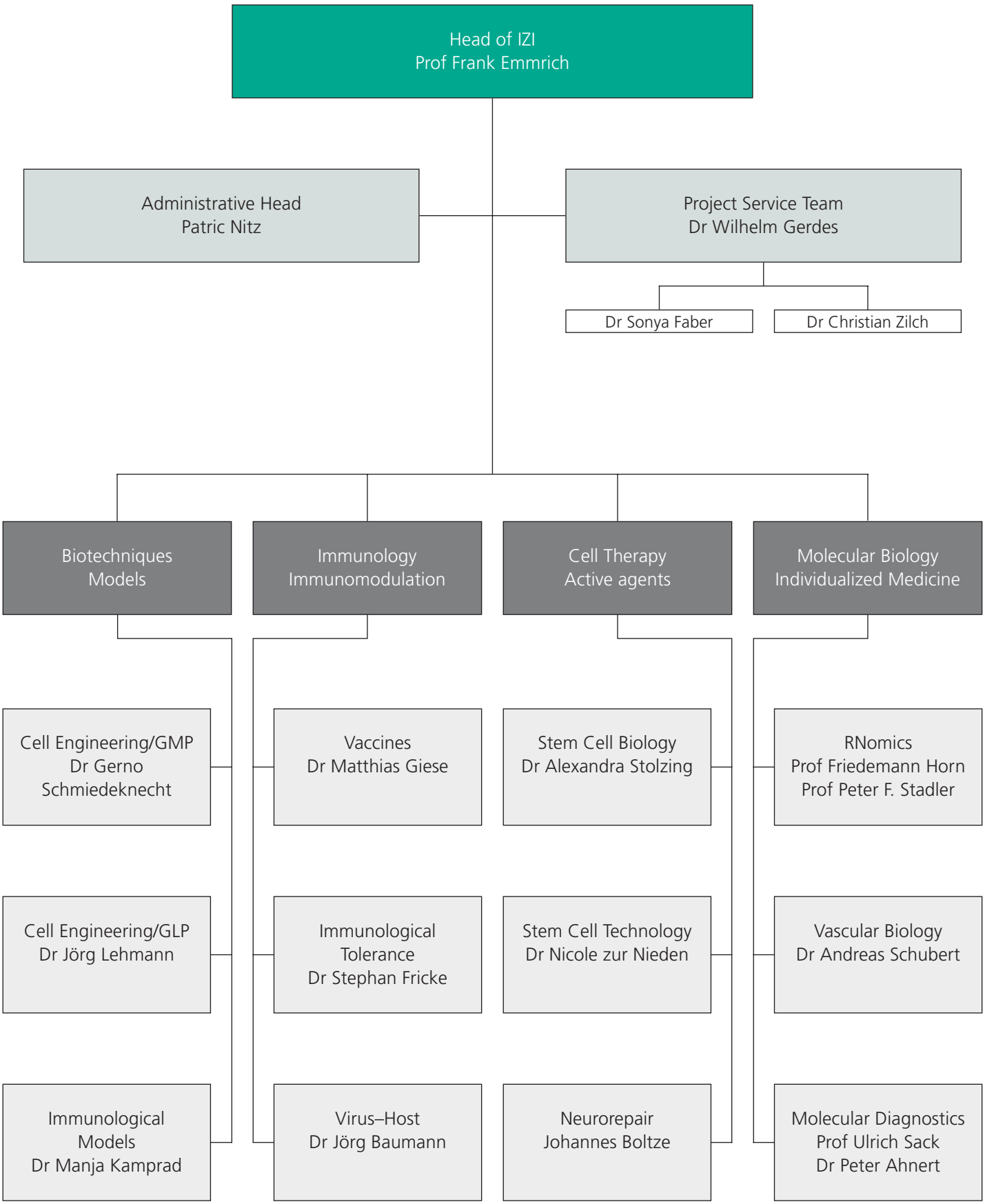
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Active agents
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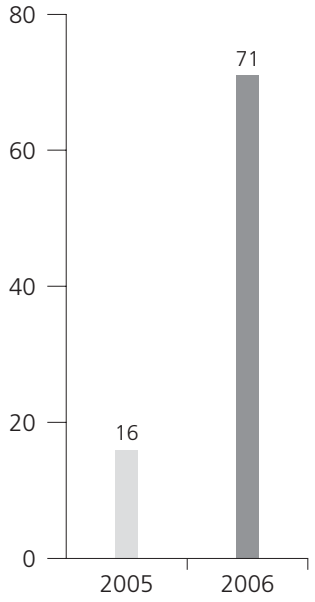
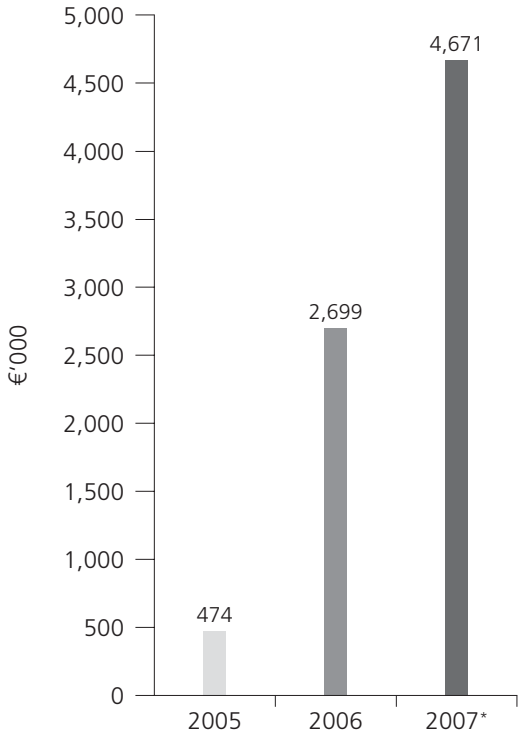
Human Resources

After starting in 2005 with a small group of 12 members of staff and the support of university institutions, by late 2006 the number of people employed by IZI had risen to 71 (a figure which is steadily increasing). The total staff of 71 comprises 58 full-time staff, 7 visiting scientists and 6 temporary staff taken on for less than three months. Women make up 60% of the workforce. Apart from the administrative manager, the core of the administration consists of four members of staff, including one in charge of facility management. Thanks to an employee who had already been employed in the financial Department of another Fraunhofer Institute, the Sigma-System used throughout the Fraunhofer Society for financial administration was quickly introduced.

Employees

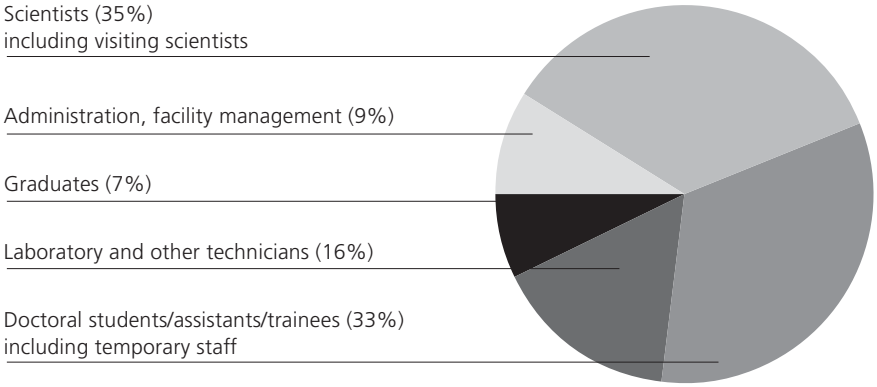


Revenue



* Funding already acquired for 2007

Employees in 2006



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"Lean administration and an economical approach are our motto, along with swift, precise communication for our clients and partners."

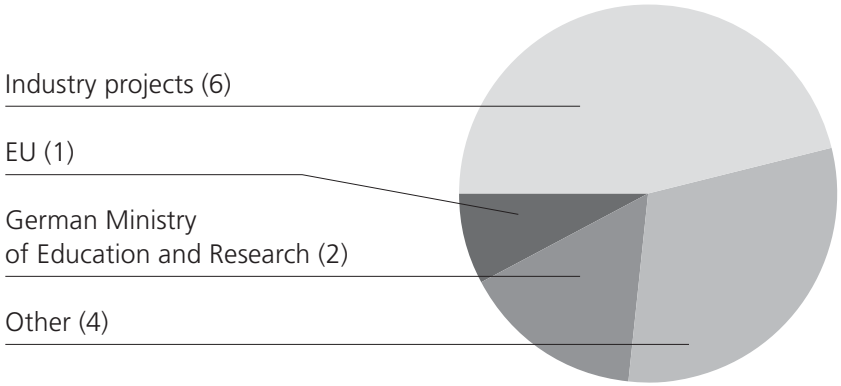
Budget

The operating budget rose parallel to the number of staff, reaching €2.7 million in 2006. Thanks to intensive project acquisition in 2006, funding totaling more than €4.6 million has been secured for 2007. The budget contains grants from the Free State of Saxony and Leipzig's Technology and Innovation Promotion Fund.

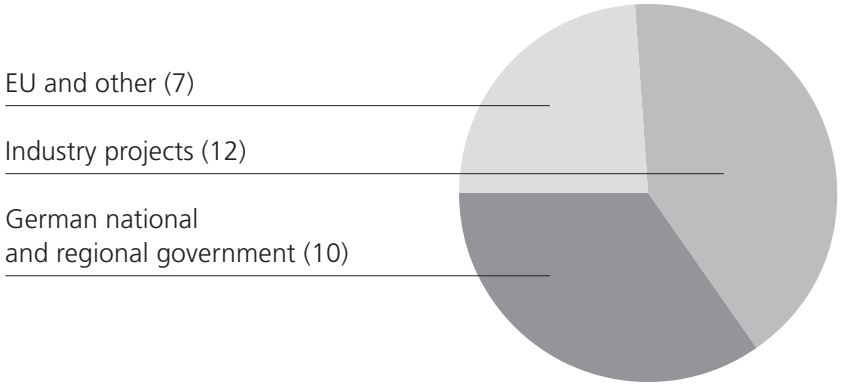
Projects

Research activities at IZI are dominated by contract research. The aim is to strike a balance between projects financed by the public sector and industry projects. In simple numerical terms this aim was achieved, although during the initial phase the funding for industry projects lagged behind the subsidies provided for publicly funded projects. Since large-scale projects with a volume exceeding €500,000 usually entail award and negotiation phases lasting several months or even a year, the groundwork was laid for a series of interesting projects in 2006 which will only be concluded in the next period under review.

Projects Contracted in 2006



Projects under Negotiation in 2006



Competencies and Technologies

IZI conducts R&D work which contributes to the identification of deficits and functional disorders in body cells and tissues as well as restoring tissue and organ functions in the widest sense by means of regenerative medicine. Accordingly, IZI supports the development, production, clinical testing and approval of diagnostic and therapeutic techniques and products that serve this purpose.

The potential clients and partners of IZI are commercial companies working in biotechnology, pharmaceuticals and biomedical engineering, hospitals and other providers of medical services, public-sector clients, and partners from university and non-university research. IZI offers its partners and clients technological expertise and innovative developments in the fields of biotechnology, immunology, cell therapy and molecular biology.

Biotechniques – Models

In this area, 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 particular material and surface properties. IZI also has special expertise in developing techniques for the production of cell and tissue cultures as well as monoclonal antibodies.

IZI's in house production facilities are designed for the manufacture of clinical trial samples. Regarding the production of antibodies, IZI is also skilled in the downstream processing of raw products. Cell and tissue models developed by IZI can be used for testing, screening and the immunotoxicological examination of new drugs, cosmetics, food additives and industrial chemicals. IZI offers various small- and large-animal models for therapy development during the course of the pharmaceutical development value chain.

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. IZI develops techniques to monitor immunoreactivity and to monitor unwanted responses such as GVH (graft versus host disease). It also develops vaccines on an innovative technology platform using plasmid DNA which are particularly safe, robust and inexpensive.

Cell Therapy – Active Agents

In this area, cells are developed, cultivated and bred for therapeutic purposes. 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 tumour treatment. One key area is cell-therapy techniques for ischaemic diseases such as stroke and myocardial infarction. Projects also include research into methods of preventing the degeneration and ageing of cells. Furthermore, IZI explores the 'dormant' stem cell potential and derives new strategies for drugs able to control tissue growth and regeneration.

Molecular Biology – Individualized Medicine

In the field of molecular biology, 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, IZI develops pharmacogenomic and protein-chemistry 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.

Client Care and Project Service

The Business Development/Project Service Team

The primary function of this division is business development – particularly in identifying and contacting potential cooperation partners. In addition to scientific centres and universities, the team is in contact with other potential partners which primarily include industrial companies of various sizes. Contact is sometimes made through attending trade shows, conferences and conventions. Alternatively, new contacts are developed through existing partnerships, while existing partnerships are continuously nurtured. In addition to national partnerships, the business development team is increasingly striving to set up international cooperation. For this purpose, in 2006 intensive discussions took place with companies and research groups in the Czech Republic, Indonesia, Israel, Singapore and the UK. In the coming year, additional contact in Japan and the USA are expected.

Apart from pinpointing potential cooperation partners, the team also busies itself intensively with applying for funding, for the mutual interest of its scientists and partners. It sifts through funding calls from the national and regional government in Germany as well as throughout the European Union and forwards suitable ones to the relevant groups at 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 IZI and maintains close contact with those deciding the allocation of funds at financing institutions in order to enable not just optimum communication but also the successful controlling of project documentation.

Moreover, the team members carry out representative functions – such as organizing the 1st Fraunhofer Life Science Symposium in 2006, and they also manage the public relations activities of IZI while also editing reports on behalf of the management of IZI and the advisory board.

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The Business Development Team offers IZI's partners from industry and science rapid, extensive information on the range of services offered by IZI, puts interested parties in touch with the relevant groups at IZI, and provides assistance in connection with applications and contract negotiations. Just give us a call!

Competencies and Technologies

Biotechniques – Models	Page
Bioreactor technologies for the propagation and differentiation of cells	23, 39
Technologies for embryonic, early and adult stem cells	39, 43, 30
Qualified apparatus for GLP analysis and quality control	26
Qualified systems for GMP production (cell cultures, monoclonal antibodies)	23
Conservation and storage techniques for cells and tissue (vitrification)	43, 23
In vitro cell culture models (including suitable for screening)	
Stem cells tests, e.g. embryotoxicity (correlate) assays	39
Cartilage and bone formation	43
Protease inhibitors and protein turnover	43, 55
Neuronal hypoxia on differentiated and undifferentiated cells	46
Mucosal virus transmission	37
Experimental therapy models on small animals (mice, rats)	
Acute ischaemic stroke	46
Arthritis (collagen, antigen, adjuvant)	55
Encephalomyelitis (EAE)	55
Xenogeneic and allogenic GvHD	35
Bone fracture models for therapy development	39
Diabetes mellitus	43
Salmonella enteritica infection model	49
Tumour models	43
Experimental therapy models on large animals	
Stroke in sheep	46
Paraplegia in sheep	46

Immunology – Immunomodulation	
DNA vaccines, definition, plasmid development, strategy and validation	32
Vector vaccines, development and validation	32
Analysis (including screening) of potential antiviral vaccines and drugs	37
Retroviral vectors and vector development	37
Virological work in S3 laboratory in cooperation with partners	37, 32
Antibody production (monoclonal, polyclonal)	26, 46
Diagnostic and analytical immunoassays	55, 55
Cell function tests (lymphocytes, monocytes, granulocytes), colony tests	30, 26
Immunotoxicity trials (including in screening)	26, 30, 55
Flow cytometry (analytical and preparative)	26, 30, 55
Immunohistology and immunopathology (with partners)	55
Laser-assisted microdissection	55, 26
Fluorescence microscopy and confocal microscopy	55, 30
Electron microscopy	26

Cell Therapy – Active Agents	
Cell cultivation from tissues and characterization	26, 30, 55
Cell separation (elutriation, density gradients, magnetic, sorting)	30, 55, 26
Karyotyping of cell cultures and cell lines	55
Drug development and screening	23, 26
Process development and application of cell cultures	23, 26
Experimental imaging and tracer development for cell tracking	46
(luminescence imaging, MRT, CT, PET with partners)	
Cultivation of dendritic cells for immunostimulation	46
Cultivation of killer cells for tumour therapy	46

Molecular Biology – Individualized Medicine	
Microbiology of karyogenic bacteria	49
MicroRNA technologies (including high-throughput, transcriptomics)	51
RNA structural simulations, RNA–protein and RNA–RNA interactions	51
Automated mass spectrometry of DNA and peptides (high-throughput)	55
Quantification of oligonucleotides	55, 51
Quantification of peptides	55, 26
Protein and peptide analysis (high-throughput, proteomics)	26
Protein separation and protein purification (HPLC)	26

Services

Biotechniques – Models	Page
Development of bioreactor-based methods for the propagation and differentiation of cells	23, 39
Biocompatibility and drugs studies using cells and tissues	39, 30, 43
Development of drugs for embryonic, early and adult stem cells (HSC,MSC)	39, 43, 30
Quality control for stem cell processes	43, 39, 30
Development of procedures and quality control for GLP analysis	26
Contract development of GMP methods and quality management systems	23
GMP production of cell cultures and monoclonal antibodies (§ 13 German Pharmaceutical Act)	23
R&D conservation and storage techniques for cells and tissue	43, 23
Embryotoxicity of e.g. drugs, cosmetics and domestic chemicals	39
Development and testing of drugs for in vitro cartilage and bone formation	39, 43
Development, testing and screening of drugs for protease inhibitors	43, 55
Development, testing and screening of drugs for neurodegeneration	43, 46, 30
In vitro development, testing and screening of neuroprotective drugs	46
In vitro/vivo development and testing of neuroprotective drugs (stroke, tumour)	46
Development of cell therapy for stroke, paraplegia and trauma	46
In vitro/vivo development and testing of drugs for chronic inflammation e.g. arthritis	55
Development of cell therapy and drugs for the treatment of GvHD	35
In vitro/vivo development of drugs for diabetes mellitus	43
Immunology – Immunomodulation	
DNA vaccines, R&D and validation with partners (veterinary medicine)	32
Vector vaccines, R&D and validation	32
Development and analysis of potential antiviral vaccines and drugs	37
Development and analysis of potential antibacterial drugs (e.g. salmonella)	49
Retroviral vectors and contract vector development	37
Development of cell lines as test objects and expression systems	37, 39
In vitro/vivo development and testing of antiviral therapy strategies	37, 32
Antibody production, purification and conjugation (monoclonal, polyclonal)	26, 46
Diagnostic immunoassays, contract production of antigens	55, 30, 26, 55
Contract cytokine analysis in tissue and liquid samples	30, 26
Cell function tests (lymphocytes, monocytes, granulocytes), colony tests	30, 26
Contract immunotoxicity and neurotoxicity screening	26, 46, 30, 55
Contract flow cytometry (analytical and preparative), R&D	26, 30, 55
Contract immunopathological and histological analysis and quality assurance	55, 30
Individual cell analysis (e.g. microdissection)	55, 26
Cell Therapy – Active Agents	
Development of techniques for cell cultivation from tissues	26, 30, 55
Development of techniques for cell separation and cell application	30, 55, 26
Contract karyotyping of cell cultures and cell lines	55
Drugs development and screening, cell stimulation and modulation	30, 26
Contract process development and application of cell cultures, R&D	23, 26
Contract experimental imaging and tracer development for cell tracking (luminescence imaging, MRT, CT, PET with partners)	46
Cell therapy for tumours (dendritic cells, killer cells)	46
Contract in vitro/vivo development and testing of drugs for tumour therapy, R&D	46
Molecular Biology – Individualized Medicine	
Development, testing and screening of drugs for karyogenic bacteria therapy	49
MicroRNA custom arrays, known and calculating sequences	51
Development and testing of ncRNAs as drug candidates	51
Transcriptome analyses and interpretation in ultra-throughout	51
Individual therapy sensitivity of drugs (automated mass spectrometry)	55
Quantification of oligonucleotides in bodily fluids	55,51
Quantification of peptides and peptide profiles in bodily fluids	55,26,30
Protein and peptide analysis (high-throughput, proteomics)	26
Protein separation and protein purification (HPLC)	26

Client Care and Project Service

Project Development

The Business Development Team at 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. Moreover, one of the core competencies of the team is scientific and technical consulting. In addition to many years experience of scientific work, this includes in particular an understanding of the way public authorities and commercial companies operate.

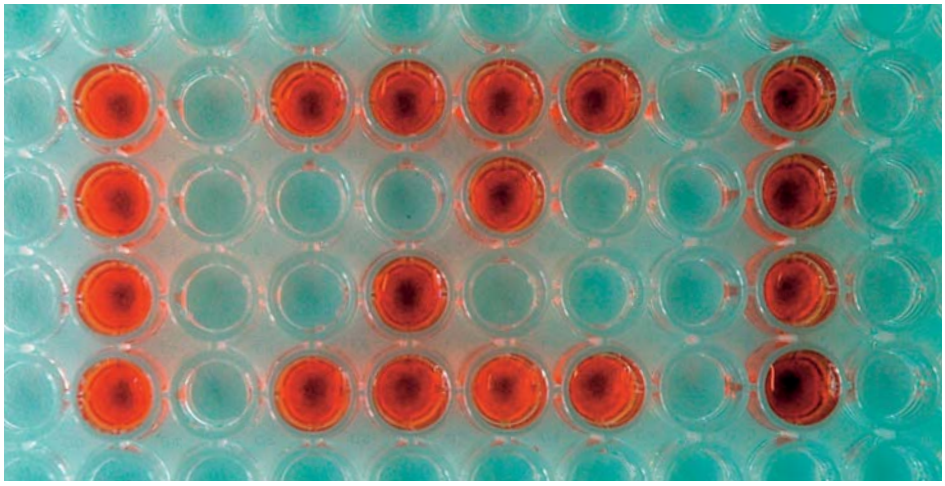
Project applications are painstakingly compiled for submission to public financial backers and industry using the internal technology platforms at IZI and the individual groups' scientific competencies. In doing so, the Business Development Team scrutinizes both the opportunities and the risks of projects and underpins applications by means of patent, literature and market research. However, the decision as to whether projects are to go ahead is ultimately taken by the client and the group leader or the management of IZI.

The key contact for project initiation is either the group leader or a member of the business development team. Both can supply the potential client with the necessary information. Assuming mutual interest in cooperation, IZI has a non-disclosure agreement or a memorandum of understanding drawn up. 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, IZI and the Fraunhofer Society.

When 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, the group leader and members of the PST write a report which is then submitted to the partner.

Project development at IZI is divided into five phases:

- Project initiation
- Production of outline and application
- Negotiations
- Project implementation
- Project conclusion

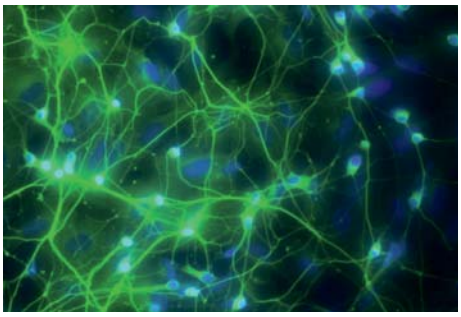


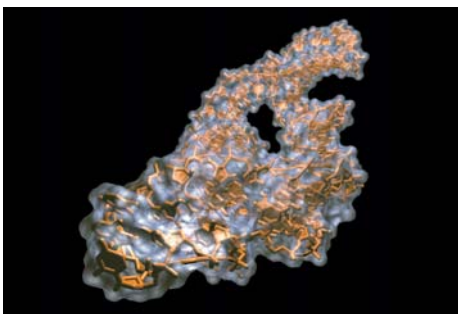
Phases of Contract Development

For contract development, IZI uses an internal road map offering maximum flexibility to the partner. The overriding principle is that of customer satisfaction, the motto being: "Customer first – company second – self third". The basic conditions and aspects of the contract are finalized in a discussion between the partners. In this early phase of contract negotiation, particular importance is attached to subsequent intellectual property and exploitation rights. Using the project outline, the duration of the contract and financial matters are discussed. In the second stage, the Business Development Team members and the IZI administrative team draw up a draft contract, which is then reviewed and if necessary modified by the project partners. In the fourth step, the application is finalized by IZI and examined by the partner's legal department. The final step is the signing of the contract by the partners.

Phase 1 Evaluation	Phase 2 Draft contract	Phase 3 Discussion	Phase 4 Finalization	Phase 5 Signing
The main points of the contract are decided by the partners (intellectual property and exploitation rights, duration of contract, financial aspects)	The first draft is drawn up on the basis of the project plan and the agreed key points	The draft contract is sent to the partner for any modifications required	Finalization by IZI; appraisal by partner's legal department	The contract is signed

Groups and Selected Projects





Cell Engineering/ GMP Group

Dr Gerno Schmiedeknecht

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Selected Project:
Cell Therapy for Parkinson's Disease

Background

Parkinson's disease is one of the most common degenerative disorders of the central nervous system. Victims suffer from muscle rigidity, tremor, and reduced mobility due to the loss of specific nerve cells in the midbrain located substantia nigra, which produce the neurotransmitter dopamine. The frequency of Parkinson's disease varies widely from one region to the next and can range from between 18 to 190 patients per 100,000 inhabitants. In Germany alone, there are estimated 300,000–400,000 Parkinson's patients. Although the pharmaceuticals currently available on the market can alleviate the symptoms for the first 5–10 years after diagnosis of the disease, their effect often fluctuates wildly. The reason is that the active agent in these drugs is not dopamine itself but rather a precursor substance. Only when the dopamine-producing cells of the patient absorb this precursor substance and convert it into dopamine are the symptoms alleviated. Whereas a healthy individual has about 800,000 of these cells, 80% of them will have died in someone suffering from Parkinson's disease by the time the first symptoms appear.

A new therapy based on allogeneic stem cells developed by the Leipzig based Biotech Company NeuroProgen GmbH is designed to directly treat this dopamine deficiency. The patient's cells which have died are compensated by human stem cells which are in vitro differentiated into dopaminergic neurons. Through the use of imaging techniques, the therapy requires cells to be deployed directly into the brain of the patient, which then produce dopamine and counteract the deficiency. In future, one single round of treatment may be enough to cure Parkinson's disease. Working closely together with NeuroProgen, members of IZI are designing a manufacturing process to bring this treatment into clinical trials.

The Cell Engineering Group operates IZI's modern GMP facility, including the separate clean room suites which have been specially optimized for the manufacturing of tissue engineering products and cell therapeutics. In addition, therapeutic monoclonal antibodies can be developed and produced in a GMP-compliant manner (including for external clients). One particular speciality of the group is the GMP-compliant production of investigational medicinal products – generally on behalf of clients and partners. High contractual flexibility is available, with for example clients themselves acquiring a manufacturing authorization and also using their own personnel. GMP-compliant process management and SOPs (standard operating procedures) are intensively discussed before being implemented. Initial reference products in the form of allogeneic somatic cell preparations for the treatment of neurological diseases are at present being developed. The staff in charge has many years of experience in designing GMP processes.


Dr Gerno Schmiedeknecht

All the members of the Cell Engineering/GMP Group undergo regular internal training as established by Chapter 2 of the EC Guide to Good Manufacturing Practice. The scope of training regarding aspects of production, quality control, procedures in the clean room and GMP-compliant documentation is specified in individually approved training plans for each member of staff.

Summary

In 2006, the Cell Engineering/GMP (Good Manufacturing Practice) Group was contracted by NeuroProgen to adapt the cell cultivation and differentiation process developed in R&D projects along with the associated quality control system to the high GMP-compliant standards for pharmaceuticals. The aim was to be granted a manufacturing authorization under Section 13 German Pharmaceuticals Act for the production of investigational medicinal products to be used in a future clinical pilot study.

Results

A number of important milestones on the road to a manufacturing authorization have already been achieved. Following the presentation of the project to the pharmaceutical regulatory agencies in charge of Saxony (Regierungspräsidium Leipzig) and Germany (the Paul Ehrlich Institute), great importance was attached to selecting GMP-compliant source materials. Since the cells come into direct contact with a large number of potentially risky animal or human substances during preparation, expansion and differentiation, the chances of bacteria, viruses or prions being transmitted must be minimized through strategic selection and special production operations.

Specifications and special test protocols were drawn up for all the source materials used to enable accurate identification and approval testing. Another essential task was the compilation of GMP-compliant documentation of the manufacturing process. Each manufacturing step was described in detailed instructions known as SOPs (standard operating procedures) to ensure the precise documentation of all the steps required in the attached protocols. Method transfer involved the production of an initial test batch in IZI's clean rooms using these SOPs, chiefly in order to create and validate the necessary quality controls.

Work then began to create the necessary quality controls, for instance determination of cell identity as well as assessment of efficacy and degree of purity. Groundwork was also performed to pave the way for the selection of a suitable procurement centre for donor tissue. Together with a tissue donation organization based in the USA, intensive work was carried out to adapt the selection of donors along with the procurement and testing of tissue to meet the stipulations contained in the current Good Tissue Practice rules (cGTP) of the Food and Drug Administration (FDA) and the European tissue directive 2006/17/EC. This provided the basis required for an inspection of the tissue donation organization by the Regierungspräsidium Leipzig and a necessary inclusion in the manufacturing authorization.

Potential

Owing to the lengthy, highly complex manufacturing process involving a number of critical source materials, the technically sophisticated quality controls, the allogeneic origin and the sensitive site of application, manufacturing this cell therapeutic involves new technical and regulatory territory.

As a result, the GMP team at IZI is qualifying itself as a competent partner for the GMP-compliant performance of complicated cell therapy projects. 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.

Project Partner

– NeuroProgen GmbH, Leipzig

Project Funding (Financial Backers)

– NeuroProgen GmbH
– Leipzig Innovation and Technology Transfer Foundation

Competencies

– GMP manufacturing of various autologous and allogeneic cell therapy products e.g. tissue engineering products, adult stem cell preparations, cancer vaccines, gene therapeutics
– GMP manufacturing of biologics using mammal cells on the scale of Phase I and Phase II clinical trials (upstream und downstream processing of therapeutic monoclonal antibodies and recombinant glycoproteins)

Equipment

– Class A (100), B (100), C (10,000) and D (100,000) pharmaceutical clean rooms with a total area of 450 sqm, modular structure, divided into suites with separate air filtration and qualification

– Qualified equipment for the production of cell therapeutics, e.g. particle-monitored class II laminar flow workbenches, CO_2-incubators (some with oxygen regulation), refrigerated centrifuges, inverse microscopes, controlled rate freezer for cryopreservation of cells, storage tanks for the storage of cells in the vapor phase of liquid nitrogen, etc

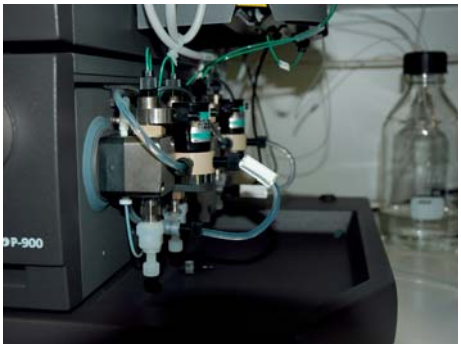
– Qualified equipment for manufacturing of therapeutic antibodies and recombinant glycoproteins, e.g. 100-litre BioWave 200 SPS bioreactor, FlexStand™ manual cross-flow filtration device, ÄKTAcrossflow automatic cross-flow filtration system, ÄKTApilot chromatography system

Products and Services

– Consulting regarding the set-up and validation of GMP-compliant manufacturing processes and quality controls as well as obtaining manufacturing authorizations pursuant to Section 13 German Pharmaceuticals Act
– Scale-up of projects from R&D to a GMP-compliant pilot production process (process development)
– Assistance in setting up a quality assurance system pursuant to the EC Guide to Good Manufacturing Practice
– Provision of separate clean room suites where project partners can manufacture investigational medicinal products in accordance with Section 13 German Pharmaceuticals Act at their own pharmaceutical responsibility and under their own manufacturing license

Cell Technologies/ GLP Group

Dr Jörg Lehmann



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Selected Project 1: Biomarkers for Rheumatoid Arthritis

Background

The demographic developments in the industrialized world are turning often crippling chronic inflammatory diseases such as rheumatoid arthritis into a growing socioeconomic problem. Currently 1% of the world population suffers from RA – and this proportion is rising. Since RA cannot yet be cured (currently, only the symptoms can be treated), diagnosing it as early as possible and differentiating it from other diseases with similar symptoms is a major aim of research in RA. Moreover, discovering new therapeutic targets and new markers for therapy monitoring would be an important step in the fight against RA.

Summary

The Cell Technologies/GLP Group, which is involved in both internal research projects as well as industry contracts, is identifying new biomarkers for two chronic inflammatory diseases: RA and Crohn's disease. In co-operation with local partners, the goals are to find and validate a technological and competence platform for the focused discovery of new diagnostic and therapeutic markers (chiefly at the protein level) for both diseases to be turned into viable strategies. Particular attention is paid to developing specific monoclonal antibodies as well as the development of simple yet robust antibody or peptide arrays for point-of-care diagnosis and therapy monitoring. The methods used to validate markers include immunological (flow cytometry), immunochemical (western blot, ELISA) and protein-chemical techniques (SDS-PAGE, 2-D electrophoresis). The biomarkers identified are mainly to be used for diagnosis in modern biochip technology such as antibody arrays. Another key aim of the entire project is to establish a biobank where biopsy material and blood from patients suffering from RA or Crohn's disease, patients with other diseases relevant in terms of differential diagnosis, and normal donors can be stored under GLP conditions following full characterization.

The Cell Technologies / GLP Group develops expertise in GLP-compliant preclinical analysis and diagnosis in the fields of immunology and cell biology. In addition, it discovers and categorizes new biomarkers for autoimmune diseases and chronic inflammations such as rheumatoid arthritis and Crohn's disease. In this regard, the group has wide-ranging technological experience in the production and characterization of new monoclonal antibodies.

Results

While seeking new biomarkers for chronic inflammatory diseases, important methods such as flow-cytometric multiparameter analysis have been established. Moreover, the infrastructure for the biobank – an essential basis for the biomarker project – has been created and key logistical questions concerning the procurement and storage of samples have been solved.

Potential

The project provides a model for the identification and exploitation of biomarkers for malignant tumours. Furthermore, work has begun on establishing an immunotoxicological and a neurotoxicological test battery based on validated, well-defined in vitro markers.

Partners

During the project, co-operation has been launched with the Institute of Bioanalytical Chemistry, Centre for Biotechnology and Biomedicine, Leipzig University (Prof Ralf Hoffmann), the Department of Proteomics of the Helmholtz Centre for Environmental Research Leipzig (Dr Martin von Bergen) and various clinical partners (Dr Maria Biskop, Leipzig; Dr Roger Scholz, Leipzig; Prof Jörg Emmrich, Rostock; Dr R Kuchta; Leipzig).

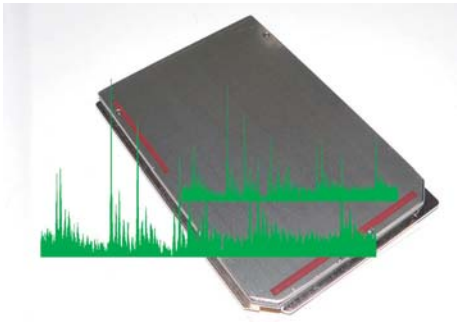
Selected Project 2: Tumour Markers in Breath Condensate

Background

Twenty-five per cent of all malignant tumours are bronchial carcinomas. In males, bronchial carcinoma is the most frequent type of cancer worldwide. And although in Germany it occurs less commonly than prostate cancer and cancer of the colon, from the mortality rate is still higher for bronchial carcinoma than from any other type of cancer. The incidence of bronchial carcinoma is about 60 cases per 100,000 people in Central Europe while the number of newly diagnosed cases (about 50,000 annually in Germany) is on the rise.

Every year, 40,000 people die of bronchial carcinoma in Germany alone, making it the fourth leading cause of death among the population as a whole – and the third leading among males. Patient life expectancy depends on the stage of the disease (TNM classification) and the subtype. Yet despite intensive research, bronchial carcinoma still has a poor prognosis and is one of the most frequent causes of tumour-related death. Early diagnosis is difficult because the symptoms mainly occur only at a late stage. There is hence a need to develop screening methods which can be used to examine groups of high-risk patients.

Most of the examination methods used are invasive (e.g. bronchoalveolar lavage fluid and fluorescence bronchoscopy) or entail considerable radiation exposure such as 'low-dose' computed tomography. Other sensitive methods of detection such as magnetic resonance tomography and positron emission tomography require extensive technical facilities and are very expensive. Although automated sputum cytology would be a suitable method, collecting sputum



is not always easy. Moreover, the algorithms for automatic/automated evaluation require further validation. Consequently, we believe breath condensate to be unparalleled when it comes to detecting non-cellular parameters.

		Lung disease	
		Bronchitis	Bronchial carcinoma; initial diagnosis
Molecular diagnosis techniques	Angiogenesis markers	Low	High
	Inflammatory cytokines	High	Low

Summary

In 2006, the Cell Technologies / GLP Group pursued three key aims: (i) establishing a multiplex sandwich ELISA (immunoassay) to validate one or more predictive angiogenesis factors in breath condensate; (ii) establishing a corresponding bank of breath condensate samples; and (iii) developing and validating a system for point-of-care diagnosis.

Results

During the period under review, the collection of breath condensate was commenced for four differential cohorts (initial diagnosis of bronchial carcinoma; progression of bronchial carcinoma; COPD – chronic obstructive pulmonary disease; healthy volunteers) using EcoSreen®. Numerous proteins can be detected in breath condensate and used for diagnostic purposes, including cytokines and mediators of angiogenesis. During preliminary work it was found that the volume of angiogeneic factors rises in connection with lung disease, although the resolution of concentrations in the pleural effusion is unpersuasive. By contrast, initial examinations of breath condensate have shown the sharpness of separation to be very good in untreated bronchial carcinoma patients. This corresponds to the typical situation during primary screening or in the doctor's waiting room, with patients suffering complaints calling in for diagnosis with relatively uncharacteristic symptoms.

Potential

Judging by the results achieved, this diagnosis technique could enable a malignant event to be identified early on non-invasively and without radiological intervention.

Successful use will depend on being able to discriminate each pulmonary aberration from a space-occupying process in the lung. The technique to be developed must be sufficiently user-friendly to rule out incorrect operation. Moreover, it must provide a result that enables a clearly defined diagnosis. Eventually, the suitability of the system is to be tested on a relevant clinical group so that, assuming subsequent trials run smoothly, a marketable product can be produced once the project is complete. One main problem is developing and optimizing a technique that enables the vascular endothelial growth factor (VEGF) in breath condensate to be measured without the need for concentration beforehand. Parallel to this, suitability is to be validated in tumour primary screening so that the diagnostically relevant decision area can be validated.

Project Partners (Selected)

The research project applied for is to be conducted with the involvement of four mid-sized pilot companies and a private doctor's praxis. The pilot companies are:

1. GA Generic Assays GmbH (Dahlewitz) – development, production and sale of in vitro diagnostic agents for autoimmune diseases

2. Medipan GmbH (Dahlewitz) – development, production and sale of in vitro diagnostic agents for thyroid diseases and type-1 diabetes

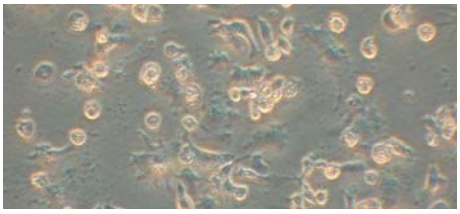
3. Kapelan GmbH (Halle) – entire logistical trial and validation system for the development and testing of diagnostic systems (also software development and internet technology)

4. Innomed GmbH (Leipzig) – performance of clinical trials (in this project: sample procurement from healthy volunteers)

Competencies

- Flow cytometry (multiparameter analysis)
- Cell separation (MACS, Dynal, CellCellector™)
- Proteomics (1-D, 2-D electrophoresis, DIGE, and western blotting)
- Protein purification (preparative HPLC) under GLP standards
- ELISA technologies
- Platform for the development of polyclonal and monoclonal antibodies with hybridoma selection via methyl cellulose

- Development of in vitro assays
- Salmonella enterica infection models in the mouse
- Autoimmune models in the mouse (rheumatoid arthritis, Crohn's disease)
- Spectrophotometer (visible light, UV; Analytic Jena Specord 40)
- Real-time thermocycler (96-well plate; Roche LC480 instrument)



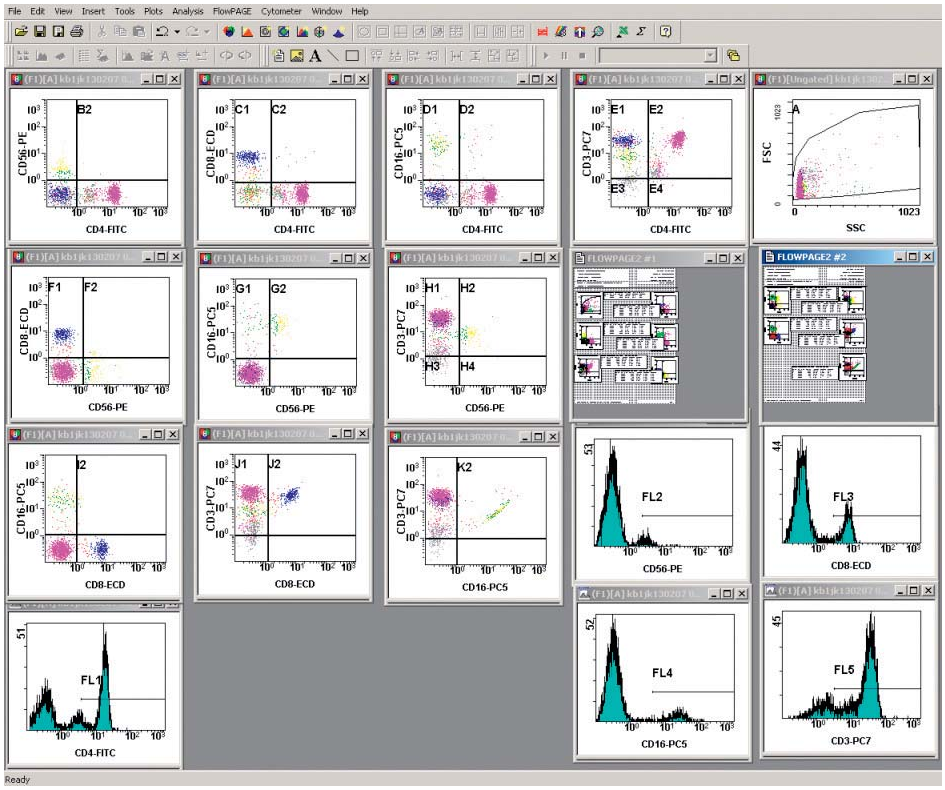
Mouse cell lines seen through a microscope

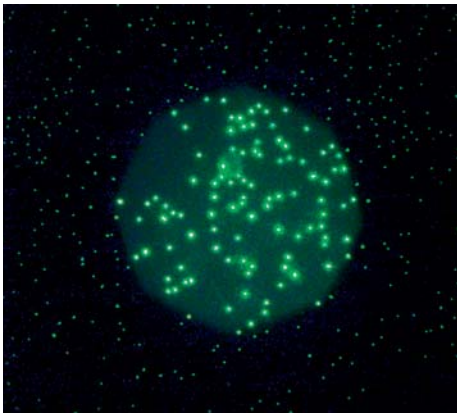
Equipment

- Fully equipped GLP laboratory
- Beckman Coulter flow cytometer (Cytomics FC500, EPICS XL)
- Magnetic cell separation (MACS, Dynal)
- Automatic cell separation (AVISO CellCellector™)
- Multifunctional plate photometer (visible light, UV, fluorescent light, fluorescence polarization, chemical luminescence; Tecan Safire 2)
- Protein purification (Äkta Purifier), HPLC

Products and Services

- Production of monoclonal and polyclonal antibodies
- Purification and conjugation of antibodies
- Characterization of antibodies
- Production of native and recombinant antigens
- Assay development (ELISA, cell-based assays)
- GLP trials (immunotoxicology, neurotoxicology)
- In vitro and in vivo studies to clarify the mechanism of vaccines and pharmaceuticals
- In vitro and in vivo testing of anti-infectives and potentially immunotoxic substances (mouse models)
- Testing of potential therapeutics with indications for Crohn's disease and rheumatoid arthritis in specialized mouse models





Fluorescent nanobeads

On-screen evaluation of FACS (fluorescence activated cell sorting) analysis

Immunological Models Group

Dr Manja Kamprad

Background

Traditional sources of stem cells for regenerative therapies such as bone marrow, peripheral blood, and umbilical-cord blood contain a low amountof 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. 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 proven to be 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 the typical mesenchymal characteristics of stem cells. 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

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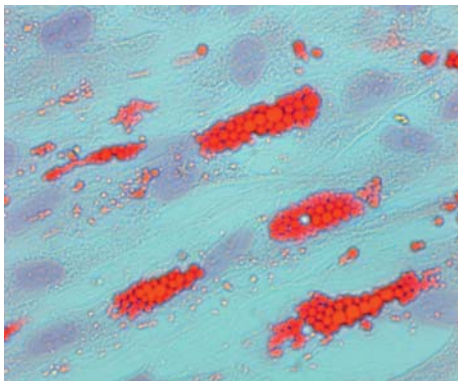
The competencies of the Immunological Models Group comprise the isolation and expansion as well as the phenotypical and functional characterization of mesenchymal and haematopoietic stem cells. Animal models are available for the conclusive functional testing of stem cells. the group managed to establish a working human immune system in mice on the basis of stem cells. In cooperation with the University of Leipzig, this model is now available for the development of therapeutic procedures. Augmenting the range of services available from the Molecular Diagnostics Group, immunocompetent cells are extensively characterized in terms of both phenotype and function.

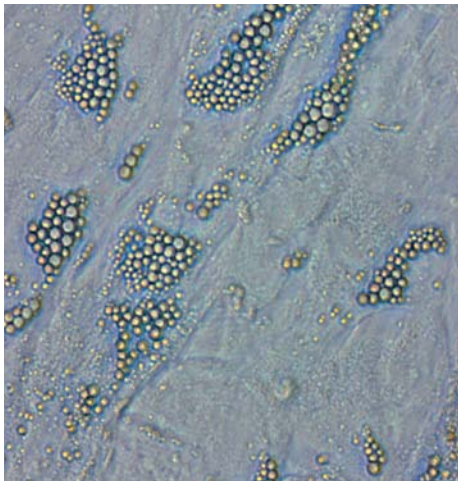
into old age is especially significant for autologous regenerative treatment strategies.

Project Partners

- AG Neuroreparatur (IZI) – neuronal ischaemia
- Vita 34 AG, Leipzig – development of cell therapeutics
- Pluristem Inc., Haifa, Israel – evaluation of cell therapeutics



Adipocytes with fatty inclusions [red]; cell nuclei shown in blue



The in vitro development of fat cells from mesenchymal cells takes about three weeks. The cell bodies are filled with fat droplets. The figure shows a light image of unstained cells

Project Funding

- Sächsische Aufbaubank Dresden (Saxony Development Bank)
- Pluristem Inc.

Competencies

Mesenchymal stem cells:
- Isolation, expansion, phenotyping, in vitro differentiation (adipocytes, osteoblast/osteocytes, chondrocytes), inhibition of MLR

Haematopoietic stem cells:
- Isolation, expansion and phenotyping of haematopoietic stem cells, determination of colony-forming cells, proof of the haematopoietic reconstitution ability in animal models (immunodeficient mouse)

flow cytometry:
- Multiparameter flow cytometry analyses as vitality tests, apoptosis/ necrosis tests, cell cycle analyses, expression analyses (intracellular and membrane-bound)

Functional testing of immunocompetent cells (lymphocytes, monocytes, granulocytes):
- E.g. LTT, chemotaxis, phagocytosis, respiratory burst activity, release of immunoglobulin, cytokine and leukotrienes, cytotoxic activity of natural killer cells

Determination of serological and cellular immunodiagnostic laboratory parameters in patients (clinical immunodiagnostics in cooperation with the University of Leipzig):
- E.g. lymphocyte subpopulation, subtyping of dendritic cells and natural killer cells, B-cell maturation status, CAST, detection of cytokines and growth factors

Equipment

Analysis:
- Flow cytometer (4/6 colour)
- Inverse fluorescence microscope with digital imaging and processing (including ApoTome slider module)

Assays:
- Fluorescence/chemiluminescence reader

Cell culture techniques:
- Hypoxia incubator

Products and Services

- Studying the haematopoietic and mesenchymal potential of cell populations
- Coating of surfaces using adult stem cells and derived progenitors (tissue engineering)
- In vitro biocompatibility testing of drugs and surfaces for immunocompetent cells and adult stem cells
- Biocompatibility studies in animal models (immunocompetent mouse) with particular emphasis on haematotoxic and immunotoxic effects
- Quality control of cells and cell products in stem cell assays and cell function tests
- Compatibility testing for mesenchymal and haematopoietic stem cells as well as immune cells e.g. of drugs, surfaces, scaffolds, cosmetics, vaccines and food additives
- Composition analysis with respect to cytokines in biological fluids

Vaccine Development Group

Dr Matthias Giese

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Selected Project 1: 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 lots of 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 migrating 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 proportion 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.

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.

Summary

The objective of the project/ programme is to study the spread

As its name suggests, the Vaccine Development Group develops marker vaccines for veterinary medicine. DNA and vector vaccines are a new technology that provide effective protection against infectious diseases. The activities of the group focus in particular on DNA vaccines designed to make pigs, horses and pets immune to viral, but also other infections. In addition, in January 2007 an extensive R&D programme on the West Nile virus was launched. Starting from this zoonotic pathogen, the aim is to develop a corresponding human vaccine.

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

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

Potential

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

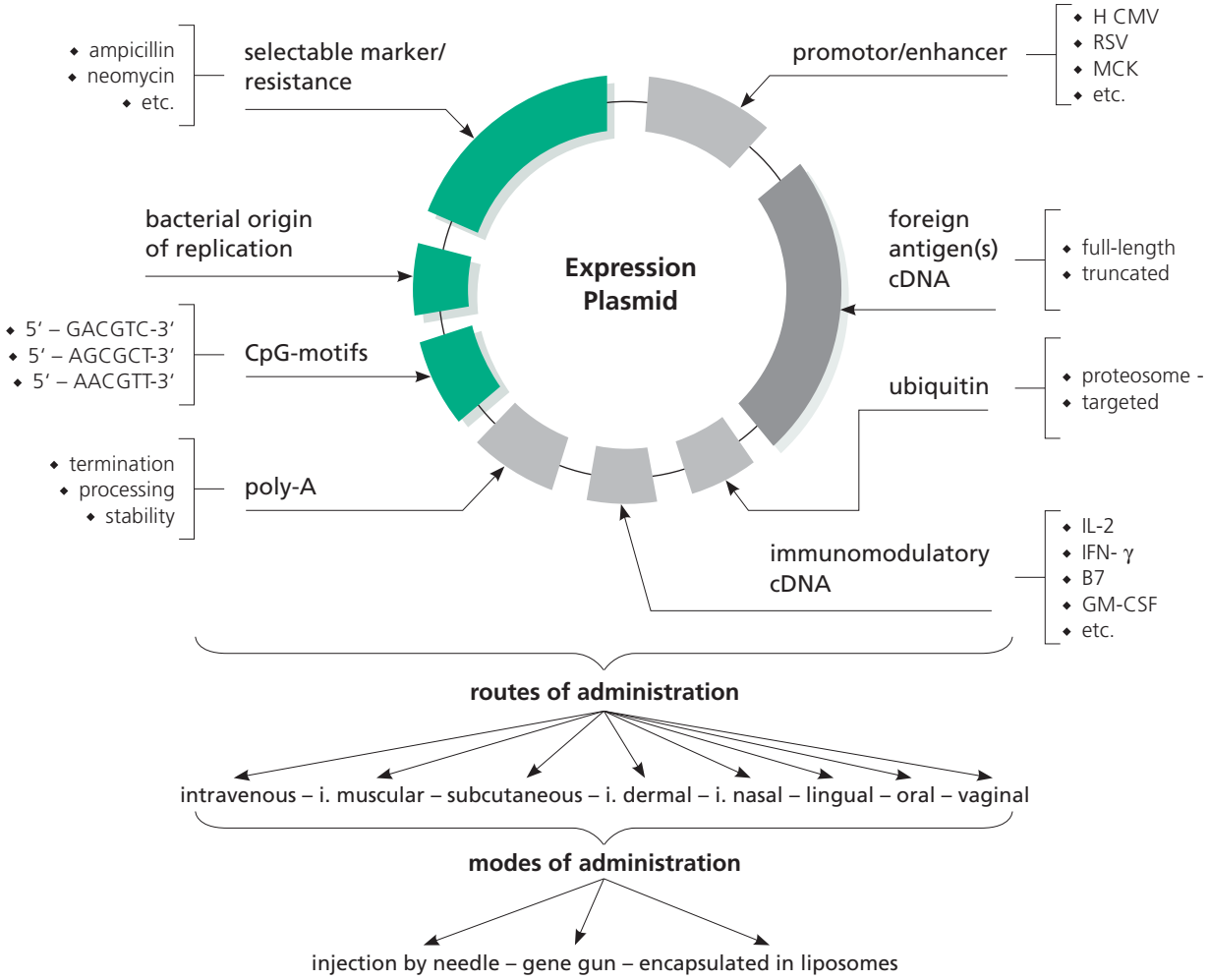

Figure: DNA vaccines*

Diagram of 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.

* Giese M. 1998. DNA-antiviral vaccines: Novel developments and approaches – a review. Virus Genes 17: pp 219–232

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 a pathogenic antigen is usually applied intramuscularly, subcutaneously or intravenously, although oral administration is also effective.

What makes DNA vaccines unique is that they partly imitate the natural infection pathway of a virus from adsorption through receptor-mediated penetration to budding on the cell membrane however, without having a pathogenic effect.

Project Funding

The WNV project/programme is as of 2007 being kindly funded by the German Ministry of Food, Agriculture and Consumer Protection. The project is being conducted under the auspices of the BLE German Agriculture and Food Agency under its innovation programme.

Competencies

- Platform technology for the development and validation of DNA vaccines
- For veterinary application (prophylactic application and also therapeutic application for different species)
- Potential for the development of similar types of DNA vaccines for human medicine

Products and Services

- R&D for DNA vaccines in veterinary medicine and pilot studies for human medicine

Immune Tolerance Group

Dr Stephan Fricke

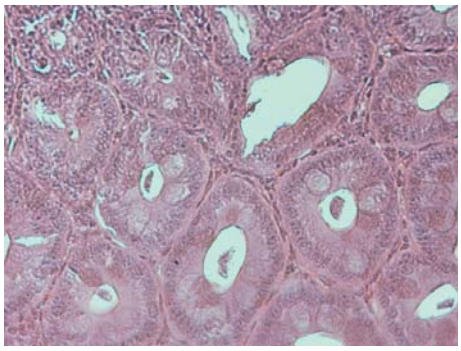

Image of the intestines in transgenic GvHD mice using light microscopic histology. Cell death was identified by plasmolysis, nuclear pycnosis, and perivascular oedema

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Selected Project: Antibodies – Induced Tolerance

Background

A haematopoietic stem cell transplant is sometimes the only way to cure leukaemia patients, and more than 60,000 such operations are carried out throughout the world annually (including more than 20,000 in Europe alone). Yet despite its notable success, this method of treatment is beset by a number of life-threatening complications, the main problem being graft versus host disease (GvHD). GvHD is caused by supravital T lymphocytes from the donor, which destroy the recipient's tissue, especially in the liver, intestine, and skin. In many cases the disease becomes chronic, resulting in severe mental strain to the patient and considerable costs for the welfare system. Following allogenic stem cell transplants, 40–70% of patients develop GvHD.

The drugs and techniques currently used to treat GvHD have several side-effects and are very expensive. A stem cell transplant costs about € 140,000 per patient – excluding any complications occurring. Moreover, taking conventional drugs to suppress immunological reactions for the rest of a patient's life, raises the risk of infectious diseases and uncontrollable tumours. Unfortunately, treating GvHD by the differential elimination of donor T cells has not been particularly successful.

Summary

New ways of controlling GvHD following a stem cell transplant while avoiding the rejection of the transplanted cells are urgently required. Both cell therapy strategies and induction treatment using anti-T-cell antibodies are therefore being used in preclinical animal models in an effort to develop a suitable method of treatment.

Results

Using a human $CD4^+$, murine $CD4^-$, human DR^+ mouse strain developed by the group, an acute xenogeneic GvHD model was established in vivo. Control mice that had not been CD4-humanized showed no symptoms of GvHD (clinical scoring and histology). Cellular markers for GvHD were determined using in vitro models.

The aim of the group is to develop ways of treating complications following haematopoietic stem cell transplants by using strategies based on cell therapy and antibodies. Both the rejection of the transplant and the undesirable cellular reaction of transplanted cells against the host organism (GvHD) need to be brought under control. New techniques have been designed based on a new type of murine/human, transgenic/knock-out GvHD model developed in Leipzig.

Dr Stephan Fricke

Potential

The findings indicate that the induction of xenogeneic GvHD is possible in the human CD4+, murine CD4–, human DR+ mouse model. Regarding the use of monoclonal antibodies for treatment, it should be borne in mind that they need to be produced specifically for different human epitopes. The humanized mouse model available in Leipzig has a number of advantages because it simulates the interaction of human cell surface molecules. Findings from the transplant model could be used for other research projects tackling immunological symptoms.

Project Partners

- Translation Centre for Regenerative Medicine, University of Leipzig
- Medical Experimental Centre, University of Leipzig
- Department of Medicine II, University of Leipzig (Haematology/ Oncology)
- Department of Radiation Therapy Clinic, University of Leipzig
- Benjamin Franklin Charité Campus, Department of Medicine III, Berlin
- Institute of Clinical Immunology and Transfusion Medicine, University of Leipzig
- Institute for Medical Microbiology and Epidemiology of Infectious Diseases, University of Leipzig

Project Funding

The project is kindly being funded by the German Ministry of Education and Research (grant no. 0313452) as well as by the project management organization Projektträger Jülich.

Spectrum of Competence

- Xenogeneic and allogenic GvHD model in the mouse
- Myeloablative und myelosuppressive conditioning protocols
- Various types of narcosis (e.g. isoflurane) in small rodents
- Production and preparation of cell transplants
- Experimental stem cell transplants and sampling: small animal model (mouse)
- Cell culture model for examining the interaction between cellular mediators
- Analysis: cell labeling, histology, flow cytometry, cytometric bead array, real-time PCR, fluorescence microscopy (all in cooperation)

Equipment

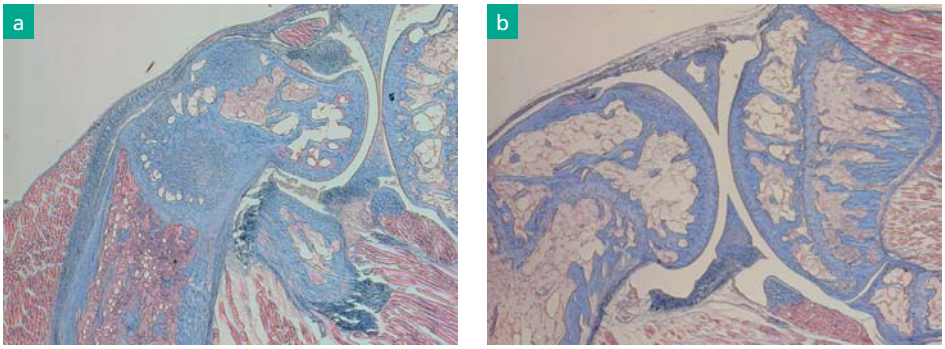
Experimental transplantation:
Instruments, facilities for operating on small rodents and taking samples; particular emphasis on cell transplants

Cell culture and analysis:
Sterile incubators for cell culture; sterile working areas for cell separation and transplant production, various microscopes for cell identification

Other equipment:
Fluorescence microscopy, electron microscopy, radiation equipment can be used in cooperation

Products and Services

- Acute xenogeneic GvHD model for testing and the screening of treatment techniques with new active agents and new types of cell therapy
- Development of myelosuppressive conditioning techniques
- Special diagnosis techniques for GvHD in experiments on animals



Morphological criteria of bone marrow cavities before and after chemotherapy demonstrate the myeloablative effect. **(a)** Haematopoietic islands with predominant erythropoiesis; **(b)** hypoplasia with significantly reduced bone marrow formation, loss of haematopoietic bone marrow, replacement by bone marrow fat cells and reduced cellularity (< 30%)

Virus-Host Group

Dr Jörg Baumann

Developing New Antiviral Strategies

Background

More than 40 million individuals world wide are currently infected with HIV (human immunodeficiency virus). Moreover, this figure rises dramatically every year, with the number of new infections up by 7 % since 2003. More than 20 million people have already succumbed to the resulting acquired immunodeficiency syndrome (AIDS). The most recent statistics testify that 1 % of the world's adult population is infected with HIV. Approved drugs to treat HIV and AIDS attack three points of the viral life cycle: the fusion of the virus particle with the cell membrane, the reverse transcription of the viral genome, and the maturation of the released particle to create an infectious virion. Due to the high rate of mutation and replication, the emergence of resistant virus populations is only a matter of time. Research at IZI focuses on the interaction of the virus with the host organism and its immune system. Our research is focused on the development of new antiviral strategies.

Summary

The launch of the Virus–Host Group at IZI in Leipzig has brought the latest expertise from the National Cancer Institute in Frederick, USA, to Germany. Cellular, viral systems and techniques within current research topics and cooperation agreements in Germany and abroad enable the group to develop new strategies to combat HIV/AIDS – from basic research to application. In 2006, the Virus–Host Group pursued two main goals as outlined below.

Results

The study of intracellular defense mechanisms against HIV has continued and has been extended to include a genetic screening method – a new experimental approach we have already employed in the USA to isolate an inhibitor of HIV replication from mouse T cells. Based on these results, strategies are now being developed to block this intracellular pathway of the virus.

In 2006, a milestone was achieved in the application of microparticles and nanoparticles in HIV research. A series

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The Virus–Host Group studies interaction between virus and host using the example of HIV. The aim is to develop new antiviral prevention and treatment strategies using the intracellular defense mechanisms of the host cell. New technological approaches enable nanoparticles to be used to control viraemia, diagnosis and therapy. A technology platform presents the development and optimization of virally based vector systems.

of different test beads was investigated in various cell culture systems, demonstrating the feasibility of the project. In forthcoming studies, the results obtained are to be verified and compared with new types of beads developed by our corporate partners.

Potential

Since antiviral strategies currently attack the virus itself, this new concept would support the current strategies. The combined therapy of HIV using drugs that, in addition to having a synergistic effect, also mutually exclude development of any new resistance mutations would be ideal. The possibility of having various drugs available that can attack the very different phases of the retroviral life cycle would expand the range of combination therapy and would be particularly useful for tackling those viral strains which exhibit a number of resistances to the drugs already used. A switch in therapy is inevitable; this highlights the need to develop new types of treatment.

The innate immune system provides the first barrier inside an organism against incoming pathogens. Recently it has become clear that mammalian cells possess a string of factors such as Fv-1, Trim5 alpha and APOBEC3G which are able to impede retroviruses following penetration of the cell membrane. These 'restriction factors' protect cells against various retroviruses and also against the reactivation of retroelements in the human genome.

However, these only recently discovered defense mechanisms are just the tip of the iceberg – there is evidence for a number of restriction factors present in mammalian cells. Working in cooperation with the HIV Drug Resistance Program at the National Cancer Institute in Frederick, USA, the group is investigating the restriction caused by a factor isolated recently by our group. The virus-host group identifies restriction factors that are expressed in different cellular systems. Similar to the currently unknown cellular cofactors, these restriction factors will be very useful for new antiviral strategies.

Furthermore, the Virus–Host Group is conducting research into the mechanism behind mucosal HIV transmission. Unlocking this mechanism would provide the basis for a possible prevention of HIV infection – something which so far has proven impossible. AIDS has now been known for 25 years – yet it cannot be cured.

Project Funding

European Commission Marie Curie Actions - Human Resources and Mobility Activity:
"New HIV Co-Factors"

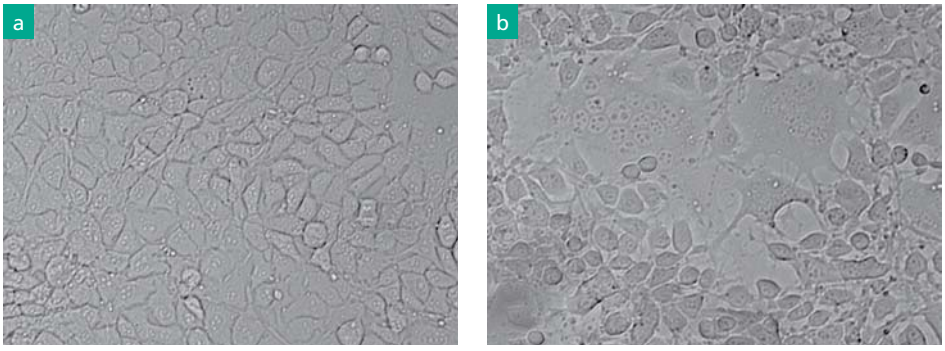
Stiftung Industrieforschung:
"Development of a novel assay to isolate HIV particles and to control HIV viraemia using a new class of micro and nano particles"

Competencies

- Analysis of molecular mechanisms in the early phase of lentiviral infection
- In vitro analysis of potential antiviral vaccines and agents
- Cell culture systems: production of diverse recombinant virus and viral vector preparations; tracking of an HIV infection in the cell using real-time PCR; cell culture system for mucosal HIV transmission; flow cytometry (with sorting option) under S2 conditions
- S3 laboratories are used in cooperation with university partners

Products and Services

- Screening of potential antiviral components (including the identification of the underlying mechanisms) in cell culture systems
- Production of tailored recombinant retroviral vector systems for aspects of basic and applied research
- Development and establishment of cell lines using retroviral vectors
- Production of standardized retrovirus batches



Cell fusions for phenotype analysis: treatment of mononuclear fibroblasts **(a)** with fusogenic substances leads to the formation of multinucleate cells **(b)**

Stem Cell Technology Group

Dr Nicole zur Nieden

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Selected Project 1: Using Pluripotent Stem Cells for the Automated Prediction of Toxic Influences on Bone Development

Background

Congenital disorders in newborns are among the most common cause of death in the first year of life. Since congenital disorders can be caused by drugs taken by the mother during pregnancy, the first step in the development of pharmaceuticals is to pinpoint any embryotoxic properties in lead substances on the basis of toxicological studies using animal tests in accordance with OECD guidelines. Unfortunately, existing in vitro assays are rarely definitive – either because their prediction reliability is low or they are enormously expensive.

Owing to their unlimited potential for self-renewal and their pluripotency, embryonic stem cells (ESCs) are a potentially inexhaustible source of cells that could be used for the preclinical screening of drugs. They are already used in industry in the embryonic stem cell test (EST), which was evaluated in an international validation study. However, the drawbacks of the EST are that the only end point currently available is cardiogenesis and that it has no metabolizing system or automation.

Summary

About half of all animal experiments are performed in order to ascertain the osteotoxic potential of new active agents. The aim of the Stem Cell Technology Group is to provide industry with an automated in vitro osteotoxicity test that is efficient and can be used routinely before new drugs are launched on the market as well as to evaluate existing ones. The acceptance within industry of an in vitro assay depends on three variables: the test must have a high predictive potential, be inexpensive, and be quick to perform. The Stem Cell Technology Group is developing an automated osteotoxicity model that uses pluripotent stem cells to assess the risk posed by substances which could prove damaging to bone development.

Results

The group has established protocols for the differentiation of osteoblasts (bone-forming cells) from murine embryonic stem cells.

The use of embryonic and early stem cells harbours a unique potential for the formation of all known tissues and organs. Cellular therapies and test systems designed to predict embryotoxicity require a better understanding of the processes subject to expansion, differentiation and apoptosis. The Stem Cell Technology Group therefore concentrates on developing cell culture techniques that enable the large-scale expansion of stem cells as well as optimization of differentiation.

Potentially osteotoxic substances can be reliably determined by taking the expression of bone tissue markers as the end point. The idea is to replace expensive traditional molecular analysis with combined automated mineralization assays. Proof of principle has been achieved on a comparative basis for six selected test substances using mouse embryonic stem cells on microculture plates. The expansion and differentiation of mouse ESCs have been established in suspension bioreactors.

Potential

The reason for introducing an automated system into an in vitro assay is to minimize human error, which would impair the model's reliability. Shortening the duration of the test, which will undoubtedly happen if new types of end points are selected, will make the method even more attractive to industry. The reliability of predictions can be raised using primate ESCs and human progenitor cells. The objective here is quite simply to completely replace in vivo osteotoxicity studies with automated in vitro assays.

Project partners

- Federal Institute for Risk Assessment (Prof Horst Spielmann, Dr Andrea Seiler)
- DASGIP AG (Dr Matthias Arnold, Jülich)
- BioE Corporation (Dr Shawn Rossi, USA)

Selected Project 2: Development of High Throughput Cultivation Methods for Stem Cells

Background

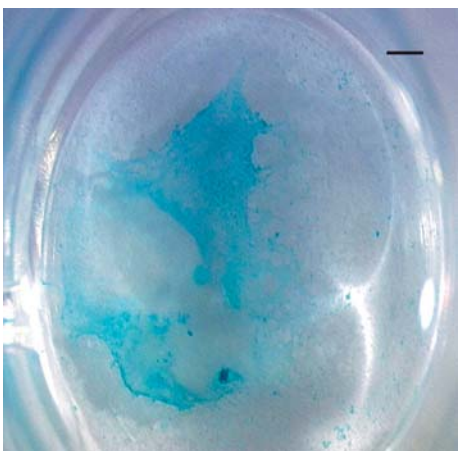
Sadly, instances of musculoskeletal diseases that attack bones and joints and lead to physical disability are remarkably common. More than half of all the people in the world suffer from rheumatoid arthritis, osteoarthritis, osteoporosis or bone injury before reaching their sixtieth birthday. Bone tissue engineering serves a broad market and can also be used to help not just humans but also animals. For example, pets – especially pedigree dogs – may suffer from considerable genetic functional disorders which impair the skeletal system and hence restrict their freedom of movement.

Regeneration disorders in the bones and cartilage have always posed an extremely daunting challenge for doctors and vets. A completely new approach is offered by tissue engineering, which can be summarized as the in situ introduction of cells able to restore the architecture and function of damaged tissue. Stem cells are especially suitable and are a new source of transplantable material for bone and cartilage engineering.

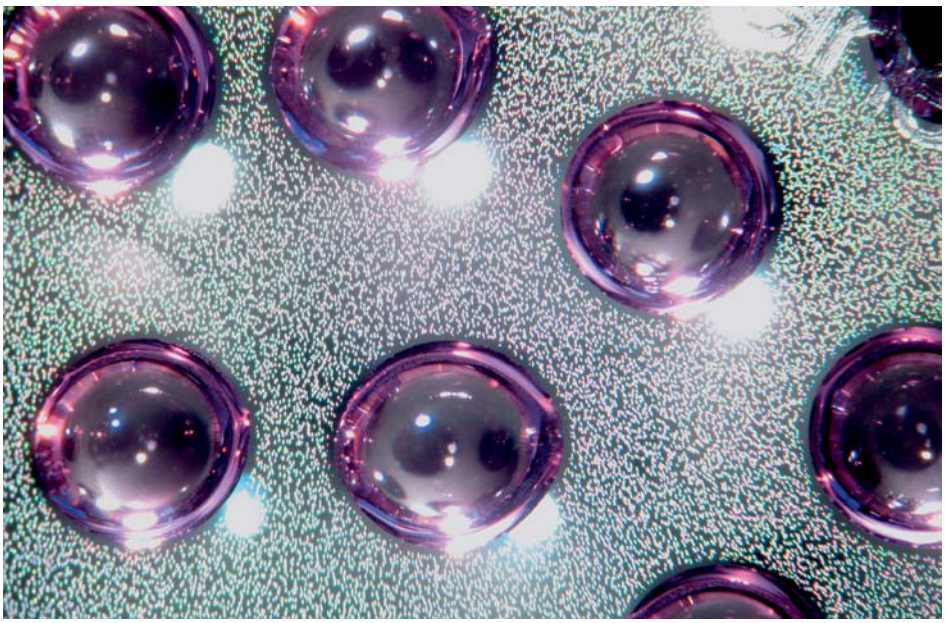
Summary

One of the biggest problems in connection with the successful

Chondrocyte differentiation of mouse embryonic stem cells (stained with Alcian blue)



Suspended droplets



clinical implementation of stem cell technologies is the cell culture methods currently used, which are insufficiently defined. More efficient methods are geared towards large numbers of cells, simplifying standardization and quality control. Scaling protocols need to be developed to increase the cellular mass available. In addition, the risk of xenobiotic products needs to be eliminated by developing serum-free media. In detail, the Stem Cell Technology Group seeks to solve this problem by automating and producing undifferentiated, early stem cells and stem cell-derived osteoblasts and chondrocytes (cartilage cells) as well as media formulations and additives which influence differentiation into osteoblasts and chondrocytes.

Results

Contrary to the general dogma, the group has managed to maintain mouse embryonic stem cells in suspension bioreactors in an undifferentiated state. The cells' pluripotency was maintained for long periods of time without any supporting materials whatsoever, while their differentiation potential was preserved and the gene expression patterns and surface antigens were also retained. Characterization work on bone formation provided indications that retinoic acid, bone morphogenetic proteins (BMPs) and the Wnt signal transduction pathway are all involved in the control of differentiation. Coupling the exogenous signal molecules led to differentiation efficiency of 90%. The differentiation of mouse embryonic stem cells in suspension into osteoblasts and chondrocytes also appears possible, the non-adherent environment boosting the efficiency of osteoblast differentiation to 98%.

Potential

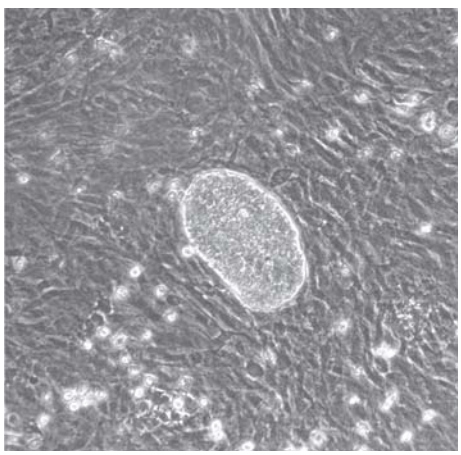
The near-clinical expansion of available stem cell material while maintaining the level of quality seems possible. It is anticipated that the protocols can also be transferred to other stem cell populations. The analysis of osteogenic differentiation shows for example that a high degree of differentiation can be achieved if suitable additives are used. Judging by the results, the cultivation and differentiation of early and adult stem cells into osteoblasts can be actively controlled.

Partners

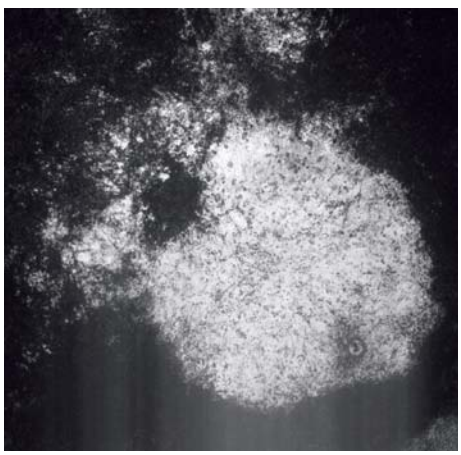
- DASGIP AG (Dr Matthias Arnold, Jülich)
- Dr Peter Horn (Hanover College of Medicine)
- Dr Erika Sasaki (Central Institute for Experimental Animals, Japan)
- Dr Irving Weissman (Stanford University, USA)
- Dr Michael Rudnicki (Ottawa Health Research Institute, Canada)
- University of Calgary, Canada (Dr Derrick Rancourt, Dr John Matyas, Dr Michael Kallos)
- Dipl-Ing Glatz (Merseburg University of Applied Sciences)
- Prof Einspanier (faculty of Veterinary Medicine, University of Leipzig)

Competencies

Process development:
Bioreactor cultivation of stem cells; optimization of differentiation protocols and medium compositions; testing of supporting materials



Embryonic stem cells from common marmosets (Callithrix jacchus) are kept in a pluripotent state on a 'feeder layer' consisting of mouse embryonic fibroblasts with the addition of basic fibroblast growth factor (bFGF)



Phase contrast image showing embryonic stem cells differentiated into bone cells

Cell culture techniques:
Expansion in bioreactors; differentiation of embryonic stem cells (neurogenesis, cardiogenesis, osteogenesis, adipogenesis); cell culture in suspended droplets

Analysis:
Genetic marker analysis (pluripotency, differentiation potential)
- CFC assay, EB assay, mineralization assays, teratoma formation
- Immunohistochemistry, immunoassays, flow cytometry, fluorescence microscopy, Western blot
- Quantitative real-time PCR (panel of 126 markers)

Signal transmission (vitamin D3, Wnt, NO)
Proliferation, migration and toxicity assays
Determination of embryotoxic substance properties

Models:
Mouse bone-fracture model

Microscopy imaging:
Mineralization quantification of bone cells by morphometric analysis

Equipment

Experimental surgery:
Systems for extensive operations on small animals in cooperation with the University of Calgary

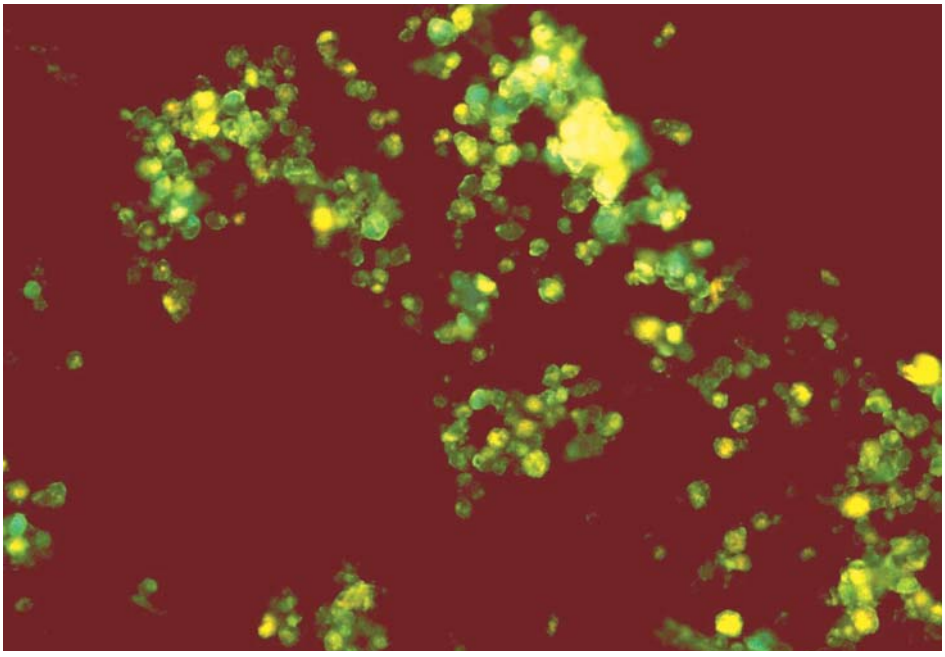
Cell culture and analysis:
Automated bioreactors (normoxia, hypoxia, online pH, temperature and gas control), flow cytometers, fluorescence microscope

Gene expression analysis:
Real-time PCR

Products and Services

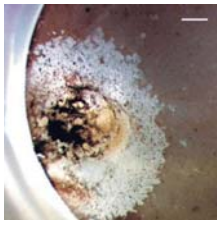
- Bone fracture models in small animals for therapy development and testing of for example cell preparation, scaffolds, active agents and delivery systems
- Testing of supporting materials (e.g. nanoparticles) for the in vitro expansion of cells
- In vitro cell culture models of embryogenesis to test the teratogenicity of active agents in for instance drugs, cosmetics, domestic chemicals, agricultural chemicals and paint
- Test systems for embryonic stem cell lines with integrated fluorescence reporters for studies, including of active agent mechanisms (e.g. for target validation and compatibility studies)
- Development of cell differentiation models

Embryonic stem cells differentiated into bone cells (tetracycline labelling)



Embryonic stem cells differentiated into bone cells (stained with Alizarin red)

Embryonic stem cells differentiated into bone cells (Kossa staining)



Stem Cell Biology Group

Dr Alexandra Stolzing

Background

Over the past one hundred years life expectancy has increased by more than 60% – and the number of elderly people will increase massively in the decades to come. Concomitantly, expenditure on healthcare rises drastically in old age. On average, about ten times more money is spent on the medical services used by an 85-year-old person than on those used by someone aged 20. In particular, age-related neurodegeneration such as Alzheimer's disease place an enormous burden on the health service and medical insurance companies, not to mention the patients themselves and their families. Initial neurodegenerative therapies already exist ranging from the use of antibodies against the protein plaques encountered in Alzheimer's to the application of substances which are anti-inflammatory and even the administering of vitamins C and E. But as the success of most therapies has been limited, we plan to test a new approach. Since microglia cells play an important part in neurodegenerative diseases, we intend to use these cells in a new type of therapy. Whenever stem cells are transplanted, it is important to make them particularly resistant to stress. This priming of adult stem cells is the Stem Cell Biology Group's main area of research.

Status

The Stem Cell Biology Group was set up in winter 2006. By the end of the year its facilities and personnel were already in place and it had all the necessary techniques at his disposal.

Summary

In autumn 2006, group head Dr Stolzing left the Centre for Biomaterials and Tissue Engineering at the interdisciplinary Kroto Research Institute and Centre for Nanoscience and Technology at the University of Sheffield in the UK. An Innoprofil application for the cryopreservation of stem cells have been submitted to the German Ministry of Education and Research. In addition, the Stem Cell Biology Group is part of a consortium which plans to research the migration and visual depiction of stem cells in the living organism as part of the European Union's Seventh Framework Programme for Research and Technological Development. Numerous

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The aim of the Stem Cell Biology Group is to combine findings from research into stem cells and ageing to create new types of therapy for tissue regeneration. It examines the ageing of stem cells and their impact on the use of adult stem cells in cell therapy. Moreover, various innovative approaches are explored in order to 'rejuvenate' adult stem cells in vitro and/or in vivo so that these cells can again become a driving force within regenerative processes in elderly patients. The group's services and competencies include measuring oxidative stress, age markers and biomarkers in cells and tissues.

Dr Alexandra Stolzing

other applications are currently being drawn up.

In addition, Dr Stolzing has authored a string of scientific publications outlining the basic ideas of the group and hence acting as a point of reference for new contacts. In connection with the above discussed problem – the development of stem cell therapies to treat age-induced neurodegeneration – preliminary experiments have already been carried out. The group has managed to demonstrate that adult stem cells can be made more stress-resistant by changing the cell culture conditions as well as using priming techniques.

Potential

Thanks to past and present research into age-related diseases, the mechanisms responsible for the characteristics of ageing are now being increasingly understood. In particular, the role of adult stem cells as protagonists of tissue regeneration harbours diverse possibilities for therapy. Accordingly, the mechanisms explored here constitute the building blocks of a platform and key technology that can be used in a wide range of regenerative therapies. As well as sidestepping the ethical problems of embryonic stem cell therapy, this approach also avoids many of the technical obstacles which have plagued tissue engineering for years. In fact issues such as the design of complicated scaffolds, the problem of scaling up adult stem cell constructs, and the complications of immune rejection can all be avoided by using the method of autologous trigger cells investigated by the group. In addition, by concentrating on microglia precursor cells and their migratory behaviour, a completely new method of overcoming the blood-brain barrier is being researched – an approach which will also be of interest with respect to pharmaceutical corporations' drug delivery technologies. The group makes use of natural cell processes in order to develop new types of therapy.

a) The use of microglia precursor cells is designed to exploit the process of cell migration for targeted regeneration pulses, especially in age-related neurodegeneration.

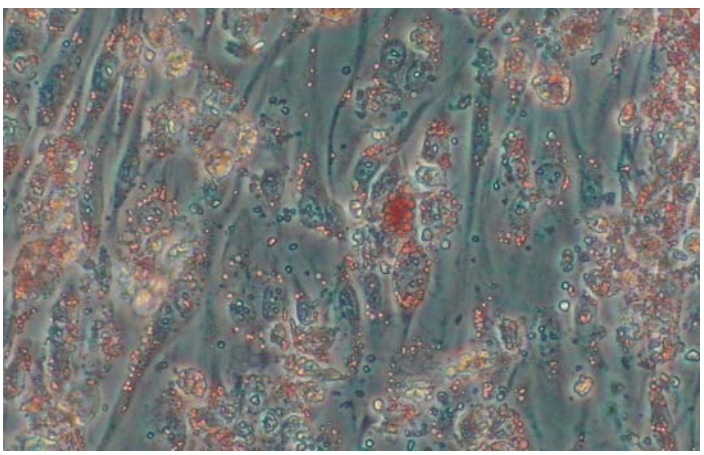
b) Processes of cell fusion can be used in vitro in order to 'rejuvenate' trigger stem cells as well as both in vivo and in situ to stimulate stem cell niches to initiate regenerative activity.

In parallel with these goals, the group is also interested in making the processes studied usable in interdisciplinary exchange with other areas, especially cell conservation, RNomics, nanotechnology and medical bioremediation. With the Stem Cell Biology Group still taking shape, its scientific profile will be decisively moulded by established cooperation and research contracts during the course of 2007.

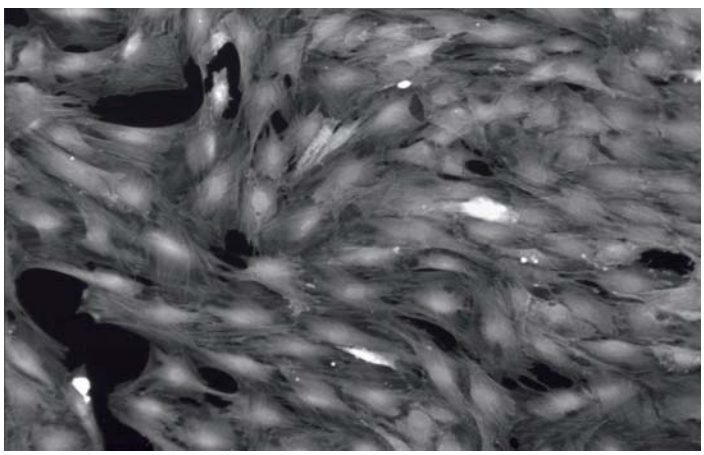
Project partners

- University of Cologne, Germany – reprogramming of stem cells.
- University of Hohenheim, Stuttgart, Germany – the impact of oxidative stress on adult stem cells
- University of Tübingen, Germany – differences between the in vitro ageing of adult stem cells and human reproductive stem cells

Human adipocytes



Human mesenchymal stem cells with stained actin cytoskeleton



- University of Leipzig, Germany
  – using new types of agonists and antagonists in the hedgehog signal pathway for the differentiation of adult stem cells
- University of Hamburg, Germany
  – ageing theories
- University of Sheffield, UK
  – development of 3D culture models for the expansion of adult stem cells
- University of Sheffield, UK – adult stem cells in diabetes
- University of Sheffield, UK
  – characterization of adult stem cells from an SOD mutant mouse
- University of Leeds, UK – ageing of human MSC
- Arizona State University, USA.
  – identification of bacterial proteases for regenerative therapy
- University of Sheffield, UK
  – proteomics of human MSC
- Paris, France – reprogramming

Competencies

Animal models:
- Ageing model (mice and rats)
- Chronic neurodegeneration (mice and rats)
- Type I diabetes (mice and rats)

Cell culture:
- Neuronal and microglia differentiation
- Cell culture: expansion and differentiation of young and old stem cells from bone marrow (mesenchymal and hematopoietic)

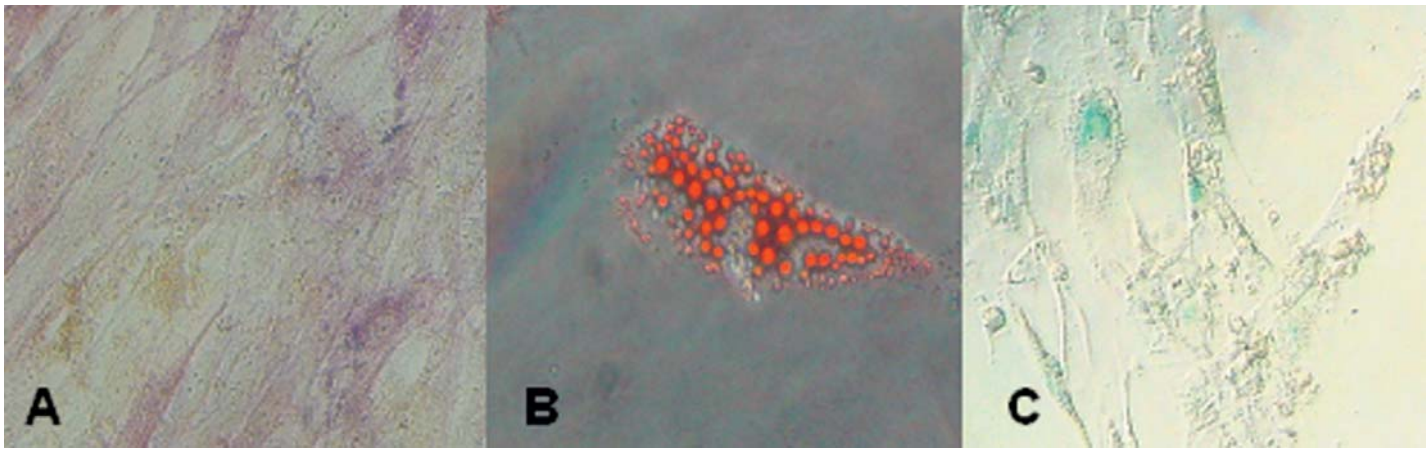
Analysis:
- Cell labelling
- Immunohistochemistry,
- Immunoassays
- Flow cytometry
- Fluorescence microscopy
- Telomere length and telomerase activity assay
- Proteasome and lysosome activity determination

Products and Services

- Screening the efficiency of new pharmaceuticals and cell therapeutic agents, especially bone anabolic agents and antioxidants in cell culture models (including as high throughput screening in cooperation)
- Differentiation analysis of adult stem cells (active agents, food additives, growth factors, stress factors, implants)
- Development of new types of cryopreservation protocols for genetically damaged stem cells
- Methods of testing the protein turnover of potentially pathogenic proteins (e.g. proteins associated with neurodegenerative diseases or AGE-breakers)
- Testing active agents as protease inhibitors

A: In vitro assay: osteogenesis of rat mesenchymal stem cells
B: In vitro assay: adipogenesis of rat mesenchymal stem cells
C: In vitro assay: Age-related beta-galactosidase expression of rat mesenchymal stem cells

Fluorescently-stained nerve cells in culture



Neurorepair Group

Johannes Boltze
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Selected Project: Treating Stroke with Cell Therapy

Background

Ischaemic stroke is alongside cardiovascular diseases, cancer and diabetes one of the main illnesses and causes of death in Germany and the USA. According to current surveys, there are about 165,000 cases of stroke in Germany every year. Following an acute stroke some 40% of patients die within the first year while another 35% are in need of constant attention. Stroke patients suffer immense mental trauma owing to the irreversible loss of brain tissue and the resulting disabilities. Moreover, stroke treatment places a severe burden on the healthcare system and social services. Yet despite intensive research endeavours, the options for treating strokes remain extraordinarily limited. Thrombolytic treatment – an attempt to reopen blocked blood vessels by pharmacological means – is administered to fewer than 10% of all stroke patients since its effectiveness is restricted to a time window of no more than three hours.

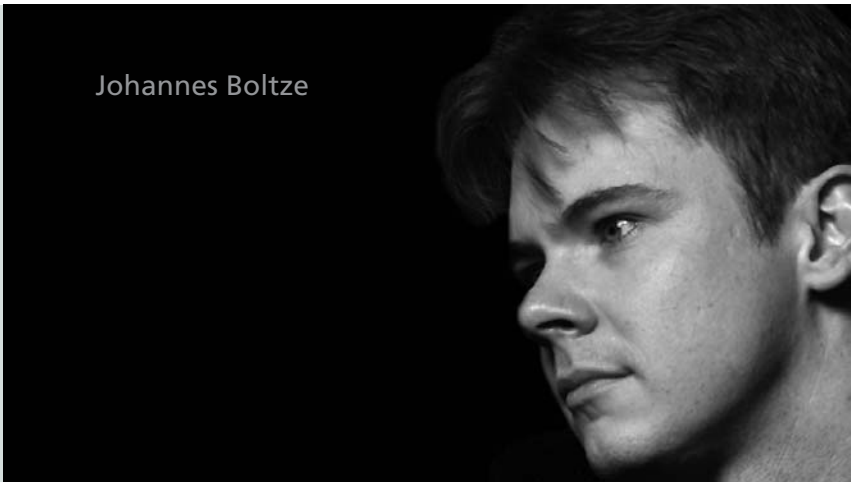
Aims

The Neurorepair Group pursued two main aims in 2006. In parallel with the conclusive evaluation of an internally developed autologous, bone marrow-based cell therapy in a large animal model in preparation for a clinical study, the group was structured such that related studies could be conducted simultaneously at any time on behalf of partners from higher education and industry.

Results

In the large animal experiments, the results of the studies on rats were confirmed through the effectiveness of the autologous transplantation of ovine mononuclear cells from bone marrow in terms of both the clinical outcome and imaging parameters (magnetic resonance tomography). In addition, other imaging technologies (such as PET – positron emission tomography) were used for experiments in the large animal model in collaboration with departments at the University of Leipzig. Comparative

The chief aim of the Neurorepair Group is to develop cell-based methods of treatment for ischaemic diseases and to elucidate the underlying mechanisms. For this purpose, three core models of cerebral ischaemia research are maintained. An in vitro model of neuronal hypoxia enables various active agents and cell populations to be screened for possible therapeutic relevance. Small animals are investigated in a rat stroke model induced through microsurgical MCAO (middle cerebral artery occlusion). Finally, an internally developed large animal model (sheep) is available for conclusive preclinical evaluation under conditions close to clinical reality.



studies in the rat regarding the use of therapeutically interesting cell populations came up with clear options for future treatment strategies. Possible cellular mechanisms of the therapeutic effect observed were identified in in vitro models.

The treatment protocol can in the future be continuously improved by harnessing these mechanisms.

The Neurorepair Group is particularly geared to contract research. A number of projects have been carried out successfully in cooperation with industry partners. Planning has also begun for a clinical trial.

Potential

Judging by the findings achieved, the success of cell therapy depends on many different factors, especially complex cell interaction between stem cells and precursor cells as well as mature populations.

Although the results also indicate that therapy in its current state of development is still limited by a time window, this window is much longer than in conventional therapy and would enable about 90–95% of all stroke patients to be treated. All in all, the identification and optimization of relevant cellular mechanisms will enable therapy to be continuously improved.

In addition, combining cell therapy with other methods of neurological intensive medicine (either experimental or already clinically established) presents interesting new approaches. The large animal model based on a sheep is an inexpensive, logistically straightforward, ethical alternative to primate models and hence constitutes an important preclinical research platform for more than just cell-based types of therapy. The Neurorepair Group's models harbour outstanding potential for adaptation to other disorders of the central nervous system such as neurotrauma. Thanks to their modular structure, the models can be adapted to each partners' needs.

Project partners

Industry:
- VITA 34 AG, Leipzig
- NeuroProgen GmbH, Leipzig
- Pluristem Inc, Haifa, Israel
- FAN GmbH, Magdeburg

Higher education:
- Faculty of Veterinary Medicine, University of Leipzig
- Radiology Centre, University of Leipzig Hospital
- Department of Neurology, University of Leipzig Hospital

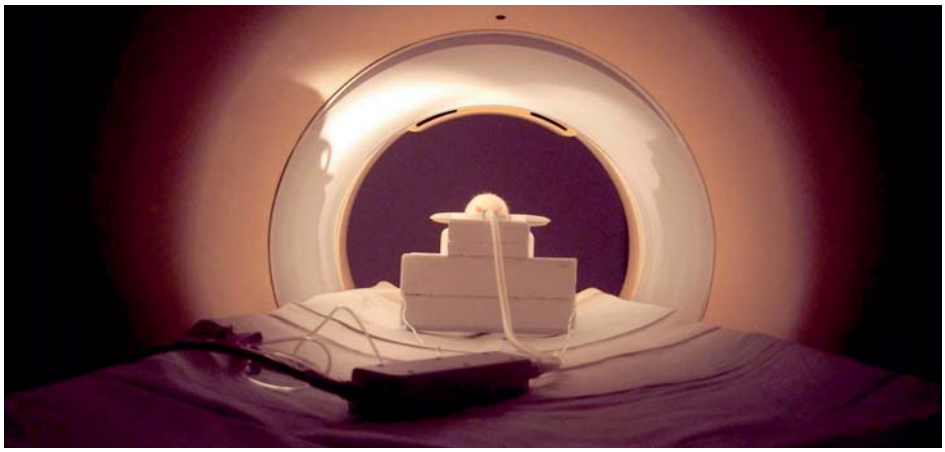
Project Funding

The project is kindly being funded under grant number 11666/1858 by Saxon development bank Sächsische Aufbaubank (SAB) based in Dresden. Research contracts have been awarded by two cell engineering SMEs.

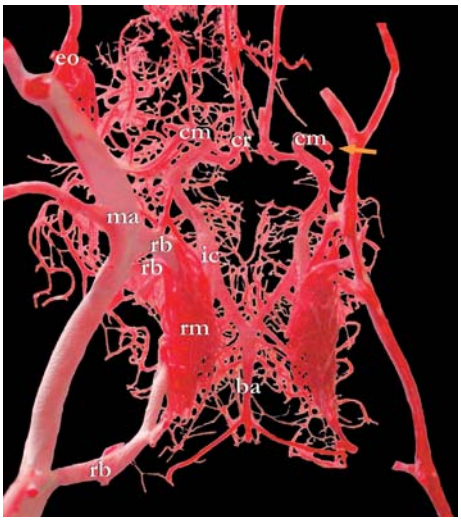
Competencies

- Animal models/stroke/MCAO (middle cerebral artery occlusion) in small animals (rats)
- Animal models/stroke/MCAO in large animals (sheep)
- Neuromotor experimental behavioural tests on small animals (rats)
- Neuromotor experimental behavioural tests on large animals (sheep)

Cell culture:
- Neuronal differentiation; cell



MRT (magnetic resonance tomography) scan of a laboratory animal



Embryonic stem cells differentiated into bone cells (stained Alizarin red)

culture model of neuronal hypoxia; expansion and differentiation of stem cells

Analysis:
- Cell labeling; MRI tracking; immunohistochemistry; immunoassays; flow cytometry; fluorescence microscopy
- MRI (magnetic resonance imaging) of a small and large animals

Equipment

Neuromotor tests:
- RotaRod, Beamwalk, stairway for small animals
- Neurological score point systems for sheep

Experimental surgery:
- Instruments, facilities and equipment for extensive macro- and microsurgery on small and large animals with special emphasis on neurosurgery

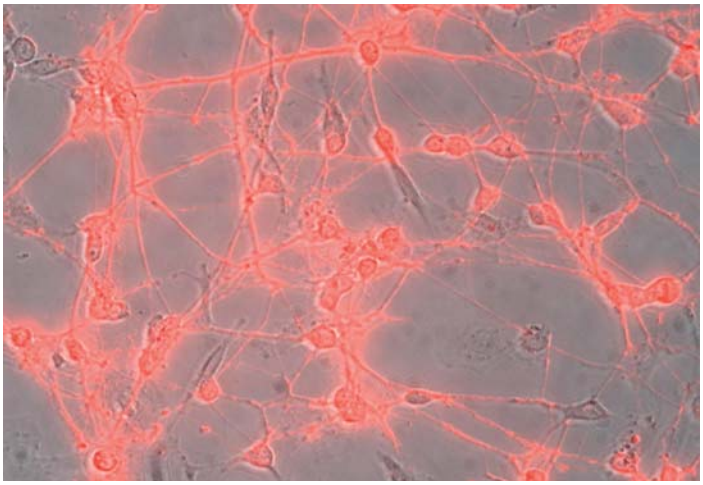
Cell culture and analysis:
- Incubators for cell culture under normoxia and hypoxia, flow cytometer, fluorescence microscope

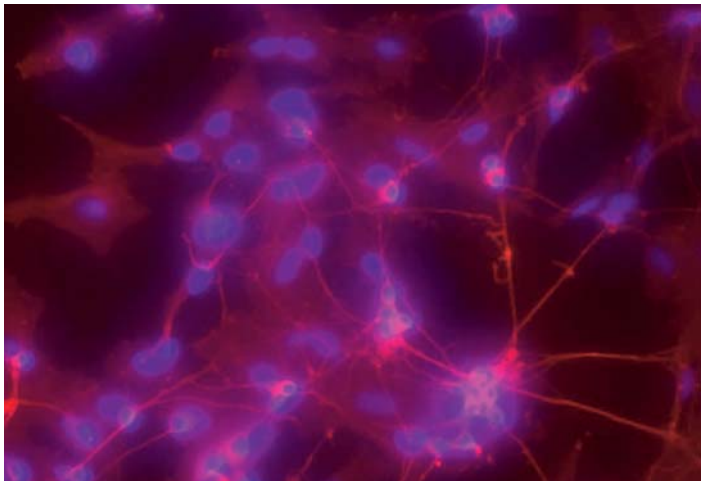
Imaging:
- Confocal laser-scanning microscope, electron microscope, MRI, PET and CT usable in cooperation

Products and Services

- Stroke models in small and large animals including multimodal evaluation (freely combinable) for therapy development (cells or active agents)
- Adaptation of models to other disorders of the central nervous system (e.g. trauma)
- Cell culture model of neuronal hypoxia to screen the efficiency of new pharmaceuticals and cell therapeutic agents
- Multimodal cell analysis and differentiation
- corrosion cast of blood vessels supplying the brain (sheep)

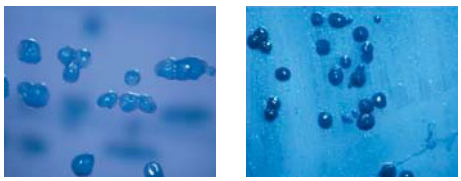
Fluorescently-stained nerve cells in culture





Vascular Biology Group

Dr Andreas Schubert



Bacterial colonies of oral streptococci

Contact

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Selected Project 1: Predilection Genes for Atherosclerosis

Background

Cardiovascular diseases are the commonest cause of death in western industrialized countries. Atherosclerosis and the associated diseases play a key role in the progress of atheromatous changes in the vessel wall. Atherosclerosis is an early form of arteriosclerosis. As arteriosclerosis progresses, the chances of heart pressure, coronary heart disease and heart attack all rise. Although the molecular mechanisms involved in the formation and localization of atherosclerotic plaques in the vessel wall have not been completely understood, they are probably connected to the functioning of endothelial cells and local flow conditions. The mechanical environment of endothelial cells is defined by complex interactions between gravitational forces and local forces (e.g. air and blood pressure) as well as intracellular strain resulting from the organization of cytoskeletal elements. Turbulent flows can mainly be regarded as pro-atherogenic and laminar flow conditions as athero-protective. Atherosclerotic changes to the vessel wall lead to increased endothelial dysfunction, the greater narrowing of the lumen (artery opening), and reduced arterial elasticity. Furthermore, the rupture of atherosclerotic plaques could lead to the occurrence of life-threatening complications such as stroke or heart attack.

Summary

The Vascular Biology Group investigates biomarkers that have been expressed early in and on cells of the vessel wall in order to determine the extent to which this vessel region is affected by atheromatous changes. In addition, the group also develops local methods of treatment based on gene therapy to prevent atherogenesis.

Results

Using human endothelial cells, the Vascular Biology Group has developed a mechanical flow model in which a number of genes have been identified

The main goal of the Vascular Biology Group is the development of prevention and treatment strategies using gene therapy for atherosclerotic changes to vessel walls. For this purpose, it has developed in vitro models for the realistic simulation of the flow conditions for vessel wall cells. The group's second aim is to develop strategies of treating dental caries and periodontosis, both of which are frequently causally related to the progress of cardiovascular diseases.

Another technological aim of the group is to develop biofunctionalized surfaces. Defined colonization surfaces are developed in 3-D structures for different cell types. Possible fields of application include cell colonization in bioreactors or on stents.

along with the putative transcription factor binding sites on their promoters. They indicate a close link to flow-related changes in endothelial cells. The gene sequences are currently being tested in suitable in vitro models with the help of reporter genes (e.g. GFP).

Potential

The economic potential of these results for the discovery of new therapy targets appears very promising. Additional studies on animal models are currently being prepared.

Project partners

Development of the in vitro vessel model:
– Leipzig Plastics Centre (Kunststoffzentrum)
– KET Liegau-Augustusbad

Modification of the surface of plastic:
– Creavac GmbH, Dresden

Higher education:
– Biofluidmechanics Lab, Charité, Berlin
– Medical Experiment Centre, Martin Luther University, Halle-Wittenberg
– Faculty of Veterinary Medicine, University of Leipzig
– Herzzentrum Leipzig GmbH – Leipzig Heart Centre

Project Funding

One area of this project (biofunctionalized surfaces) has been kindly funded under grant number KF0336301FK6 by the Berlin-based Otto von Guericke German Federation of Industrial Research Associations

Selected Project 2: Caries Project

Background

Tooth decay (dental caries or cavities) is the most frequent infectious disease in the western industrialized nations. According to WHO 2004 estimates, 80% of the world's population are affected by caries, while among school children the proportion is in the range of 60–90% depending on the country in which they live. In Germany alone, more than 95% of the population suffers from caries. It is also important to note that, that bacterial flora in the oral cavity frequently result into the progression of other, also very expensive illnesses such as arteriosclerosis and sclerosis of the cardiac valves. The health insurance companies in Germany alone spend far in excess of € 12 billion annually on the treatment of these illnesses. Therefore, establishing inexpensive methods of prevention and treatment would be of enormous significance.

Summary

IZI in conjunction with the University of Leipzig's Department of Conservative Dentistry and Periodontology has developed test systems and techniques for the in vitro testing of potential antimicrobial agents for all known oral microorganisms involved in the formation of caries and periodontosis. This led to the establishment of strategies for the focused elimination of cariogenic bacterial strains. The Vascular Biology Group is also investigating the possible determination of certain protein patterns of aggressive pathogens from dental plaque.

Results

So far, a total of 23 different types of bacteria have been identified from decayed teeth and swabs. Their pathological significance is now being comparatively studied.

Potential

The expected potential of these investigations is quite substantial and promising. This could stimulate the development of new applications in the field of oral and dental hygiene, for instance in the development of toothpaste, mouthwash and chewing gum.

Project Partners

Higher education:
– Department of Conservative Dentistry and Periodontology, University of Leipzig
– Department of Preventive Dentistry, Friedrich Schiller University, Jena
– Herzzentrum Leipzig GmbH – Leipzig Heart Centre

Competencies

Cell culture:
– Incubators for the cultivation of bacteria under aerobic and anaerobic culture conditions

Analysis:
– Real-time PCR, colony hybridization, cell marking, immunohistochemistry, immunoassays, analysis of high-throughput gene and protein expression

Products and Services

– Testing of drugs and therapeutics on cariogenic bacteria under different culture conditions
– Ascertaining anti-cariogenic mechanisms
– Optimizing antimicrobial agents

RNomics Group

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Selected Project 1: Tumour-related microRNAs

Background

Among the ncRNAs identified so far, microRNAs represent the largest class. In the human genome, they currently comprise about 500 known members. With a size of about 22 bases, microRNAs regulate gene expression at the post-transcriptional level. A major mechanism of microRNA action represents the inhibition of specific target mRNAs, caused by either an accelerated degradation of such mRNAs or a blockade of their translation.

In many diseased states, most remarkably in tumours, elevated or reduced levels of particular microRNAs were detected. Therefore, microRNA expression profiles likely provide valuable diagnostic markers for malignancies. In fact, a number of microRNAs have been recognised as key players in the regulation of tumour-relevant processes, acting as either tumour suppressor or oncogenes (‚oncomirs'). Consequently, microRNAs not only possess high potential as sensitive diagnostic and prognostic markers but some of them may also serve as therapeutic targets. As a result, these molecules attract increasing attention in the field of applied research, generating high demand for techniques for their identification, quantification, and functional characterisation. Yet, especially in oncology, this broad attention renders the situation for intellectual property rights quite difficult: many known microRNAs have already been described as disease-relevant, and inhibitors for potential therapeutic applications can be derived immediately from their sequence.

ncRNA

Of the about 3.3 billion bases of the human genome, only about 1.5% code for proteins. Recent studies have demonstrated, however, that the overwhelming, non-protein coding part of the genome is actively transcribed into RNA as well. Such non-protein coding RNAs (ncRNAs) constitute a major part of the cellular transcriptome not translated into proteins. Regulation of ncRNAs turns out to be highly cell-specific. Remarkably, many ncRNAs are found to be associated with diseases.

The RNomics Group identifies and characterises disease-associated ncRNAs as novel diagnostic markers and therapeutic targets. In developing the required techniques and strategies, the group follows a platform approach by paying particular attention to an applicability of such methods irrespective of the disease or system studied. To meet the requirements of this novel, dynamic, and interdisciplinary field of research, the RNomics Group has established competencies in both bioinformatics and experimental biology. This allows us to pursue strategies that are based on close catenation of both fields and has already proven of value internationally – as demonstrated by participation in the multinational research project ENCODE.

Summary

The RNomics Group analyses microRNA expression in tumour cells in order to provide novel diagnostic markers as well as targets for the development and testing of new drugs. To avioid the difficult patent situation, the RNomics Group focuses on methods for the identification of novel, previously unknown microRNAs. In collaboration with bioinformaticians from the universities of Vienna and Leipzig, this is done by combining bioinformatic prediction methods with high-throughput nucleic acid detection techniques.

Results

A number of technologies for the identification and quantification of microRNAs have already been established in the RNomics Group. These are used for developments and projects within the group but are available for contract research as well. In collaboration with researchers from the University of Leipzig, we discovered a deregulated microRNA that suppresses the programmed cell death in a haematological cancer (multiple myeloma) and hence contributes to the pathological, prolonged survival of tumour cells. This microRNA is currently being characterised functionally, and its suitability as a therapeutic target explored.

To detect novel, as yet uncharacterised ncRNAs, new bioinformatic tools have been developed in close collaboration with the universities of Vienna and Leipzig. In the course of these studies, several thousand novel microRNA candidates were identified. Another project conducted together with Affymetrix Inc., allowed to detect potential microRNAs by means of an unbiased method for transcript identification. In two tumour cell lines, a total of 400,000 small RNAs (both microRNAs and other small ncRNAs) were identified.

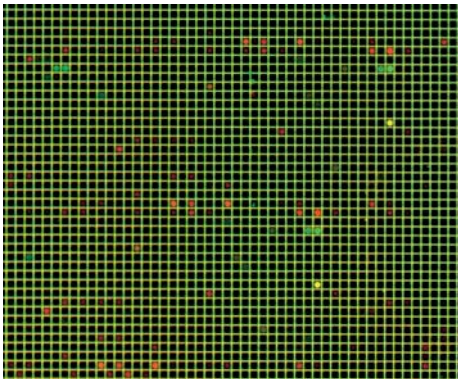
Potential

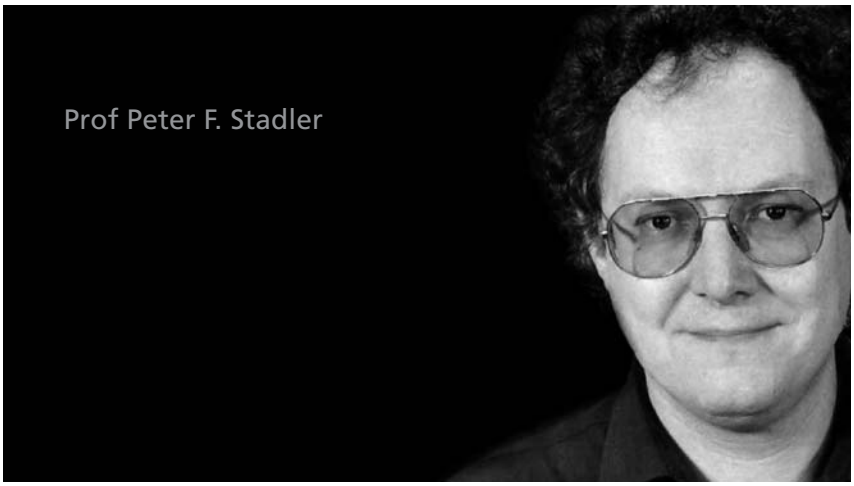
Obvious medical applications of microRNAs include use as diagnostic or prognostic markers. MicroRNAs have proven to possess high potential in preclinical trials. For example, the prostate cancer-specific transcript PCA3 has recently been recognised as a valuable marker ncRNA, and related diagnostic tools are now commercially available. In future, the RNomics Group will focus on identifying microRNAs that enable the improved classification of prostate carcinomas as a prototype application. The potential relevance of microRNAs as therapeutic targets is especially apparent for tumours. The straightforward development of antagonists such as antisense-LNAs (locked nucleic acids) should be emphasised. More complex challenges are an efficient intracellular delivery of such compounds and the currently insufficient knowledge about microRNA expression in healthy tissues. Due to numerous high-ranking publications on particular ncRNAs and microRNAs, the request for techniques to identify and quantify such RNAs is general and growing. Therefore, this field is expected to develop a relevant market for the years coming.

Project partners

- Bioinformatics Group, Department of Computer Science, University of Leipzig
- Molecular Immunology Group, Institute of Clinical Immunology and

MicroRNA array used to determine microRNA expression profiles





Transfusion Medicine, University of Leipzig
- Theoretical Biochemistry, Institute of Theoretical Chemistry, University of Vienna
- emergentec Biodevelopment GmbH, Vienna (within EU project SYNLET)
- Blue Drugs GmbH, Frankfurt (within EU project SYNLET)

Project Funding

Internal research project
Funding by EU project SYNLET, starting 2007

Selected Project 2: Unbiased Transcript Identification, Quantification and Annotation

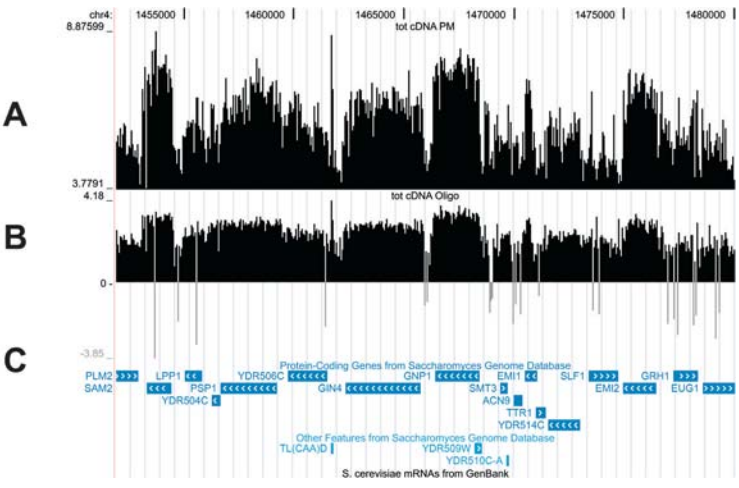
Background

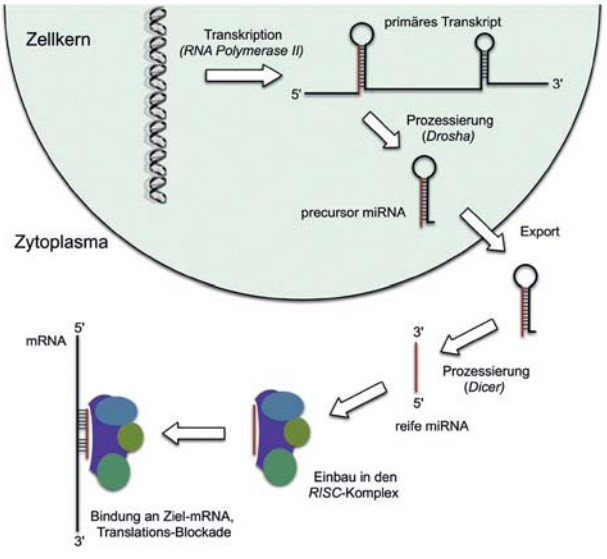
Recent transcriptome studies, e.g. within the ENCODE project, have revealed that the majority of the human genome is transcribed into RNA. Only 1.5% of the 3.3 billion bases, however, code for proteins; all others yield non-protein coding RNAs (ncRNAs). As most of these ncRNAs are as yet uncharacterised, they can be identified and quantified by unbiased techniques only, i.e. by methods that do not initially specify the transcripts they may detect. Genomic tiling arrays currently represent the most advanced method for an unbiased, genome-wide transcriptome analysis. While techniqually, genomic tiling arrays are well established, analysing the complex data obtained is still a challenge requiring considerable further developmental work to provide and optimise the tools required. Ultra high-throughput sequencing of transcripts (UHTS) represents an alternative approach for transcriptome studies. A small number of studies have recently applied the 454 pyrosequencing UHTS technology to this purpose, albeit restricted to parts of the transcriptome only, e.g. to microRNA analyses. However, new sequencing technologies are about to be launched on the market paving the way for a dynamic development of these technologies with respect to both cost and capacity.

Summary

The RNomics Group develops an efficient, reliable method to evaluate data obtained from experimental tiling array analyses. This method employs a strategy to first convert raw data into regularised signals using various bioinformatics algorithms and then quantify them. For UHTS data, a technique will be developed that allows the error-tolerant mapping of transcript sequences to the genome, followed by quantification. These methods will enable us to generate expression signals of known as well as unknown transcripts. The subsequent annotation serves to identify known transcripts and to characterise unknown transcripts as

Tilling array analysis in yeast
A Raw data **B** Curve after regularisation **C** Annotated gene structure





detailed as possible, allowing to assign transcripts to particular ncRNA classes (e.g. microRNAs) prior to experimental characterisation.

Results

For two large-scale transcriptome projects, one carried out within the ENCODE project, the other as an exploratory project led by Affymetrix Inc., the RNomics Group - in collaboration with the universities of Leipzig and Vienna - identified ncRNAs on the basis of large tiling array datasets. Among the findings of these projects (to cite all of them would go far beyond the scope of this paper), the following are of general significance: (i) the vast majority of the genome is transcribed; (ii) for the most part, these transcripts do not encode proteins; (iii) numerous long transcripts are being processed into short RNAs (i.e., approximately 400,000 short ncRNAs were detected in two cell lines); (iv) 70% of these non-coding transcripts cannot be assigned to known ncRNA classes.

Potential

Due to the growing interest in ncRNAs, there is an increasing demand for techniques that allow their identification and analysis. Genomic tiling array analyses are very ambitious both experimentally and in terms of the bioinformatic evaluation of large amounts of data. Therefore, it is anticipated that this service will be performed by specialised groups. The same holds true for the analysis of UHTS transcriptome datasets. Although (currently) this technology is still rather expensive, in the long range its potential will surpass the one of tiling arrays.

Furthermore, the data obtained from genomic tiling array analyses represent a high potential by themselves. The giant number of new, previously undescribed and mostly regulated ncRNAs represent an unprecedented opportunity to identify new biomarkers and therapeutic targets.

Project Partners

- Interdisciplinary Centre for Bioinformatics (IZBI), University of Leipzig
- Theoretical Biochemistry, Institute for Theoretical Chemistry, University of Vienna
- Affymetrix Inc., Santa Barbara, USA
- ENCODE consortium

Project Funding

Internal research project

Competencies

Transcriptomics:
- Tiling arrays (Affymetrix)
- Custom arrays (CombiMatrix)
- miRNA arrays (Eurogentec and CombiMatrix)
- High-throughput quantitative RT-PCR for ncRNAs and mRNAs
- RACE, smart PCR, and other techniques to characterise transcripts

Bioinformatics:
- Microarray low-level analysis (tiling arrays, conventional one- and two-colour arrays)
- Annotation of transcriptome datasets
- Analysis of ultra high-throughput sequencing data
- ncRNA prediction and annotation
- Prediction of ncRNA targets

Functional characterisation of ncRNAs:
- Overexpression and knock-down of ncRNAs
- Assays for ncRNA target validation

Equipment

- Array scanners (printed and CombiMatrix arrays)
- ABI Prism 7900 (high throughput real-time PCR unit)
- High-performance computing Linux cluster in cooperation with IZBI, University of Leipzig
- Affymetrix line (fluidics, hybridization, scanner) in cooperation with the Max Planck Institute for Evolutionary Anthropology, Leipzig

Products and Services

- miRNA custom array with known and predicted new miRNAs
- Identification of diagnostic markers and therapeutic targets on the basis of RNA:
  - Expression analyses of the entire genome (transcriptomics)
  - Data analysis and interpretation of high-dimensional transcriptome datasets from tiling arrays and ultra high-throughput sequencing
- Validation of ncRNAs as therapeutic targets (functional characterisation, tissue distribution)
- Development of molecular tools for the inhibition of ncRNAs and their validation as therapeutically effective compounds

Molecular Analysis and Diagnostics Group

Prof Ulrich Sack
Dr Peter Ahnert

Selected Project: Genetic Markers for the Early and Differential Diagnosis of Rheumatoid Arthritis

Background

About 1–2% of the population in the industrialized countries is affected by chronic autoimmune diseases, which in addition to causing pain and restricting mobility often incapacitate people for work and hence are a serious burden on society. One problem with chronic autoimmune diseases, especially rheumatoid arthritis, is that clear diagnosis is usually only possible once the disease has already taken hold and inflicted serious harm on the body. The therapies currently available cannot cure RA; all they can do is provide alleviation and slow down progression. In the event of very early diagnosis, however, the disease may potentially be cured. Initial, uncertain signs of RA occur in many people but only about 20% actually develop chronic RA. Since the therapies used exert considerable side-effects on the immune system and are very expensive, treating all cases of suspected RA is not an option.

Therefore, the possibility of using biomarkers for very early, reliable differential diagnosis is of high clinical relevance. Moreover, patients respond differently to different types of therapy. Although genetic variants and autoantibodies already known can make an important contribution, they are not sufficient for early, effective, individualized therapy of RA.

Summary

To make more efficient diagnoses, what needs to be done is to identify new biomarkers which either alone or in conjunction with known biomarkers will enable very early, clear-cut, individualized diagnosis so that the most suitable type of therapy can be decided. This is being carried out in association studies with markers which are disease-specific and individual-specific. Biomarkers found to be important must then be verified and validated for clinical use. Other key issues include the use and further development of modern technologies for the identification of new biomarkers and their efficient, rapid, flexible development for diagnostic use.

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The Molecular Analysis and Diagnostics Group develops rapid, straightforward immunological and genetic analyses in the field of transplant rejection and chronic inflammatory diseases, and tumors using complex cell culture models and animal experiments. The group takes advantage of the broad local network and is able to offer combined packages encompassing profile analysis of genomic expression, genetic variants and peptide patterns as well as imaging mass spectrometry.


Prof Ulrich Sack

Results

Mass spectrometry has been established and honed in the Molecular Analysis and Diagnostics Group as a flexible, powerful platform technology for measuring genetic variants, quantitative gene expression and peptide patterns. It is used for extensive genotype-phenotype association studies for RA and has enabled new markers to be identified. However, since they are not by themselves sufficient for the diagnostic applications envisaged, these markers are currently combined with known genetic markers, autoantibodies, and peptides. Moreover, the use of automated mass spectrometry has also been prepared for the determination of known, clinically relevant genetic variants.

Potential

Given the group's expertise in designing and performing studies to identify biomarkers, similar studies can be offered for diverse questions – especially projects to identify disease-relevant genetic variants and pharmacogenomics for individualized therapy and the identification of new drug targets. Such studies can also include the identification of peptide markers on the basis of automated MALDI-TOF mass spectrometry. Peptide markers identified from tissues enable imaging mass spectrometry, for example in order to identify tumor cells in tissue sections.

Project Partners

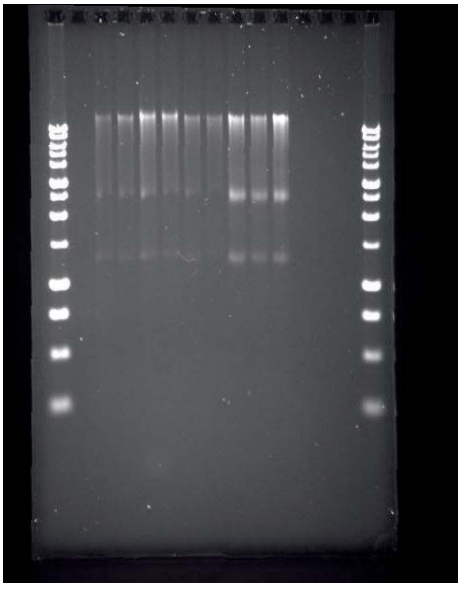
Dr Inga Melchers, genetics of systemic scleroderma and rheumatoid arthritis, Rheumatology Clinical Research Group, Albert Ludwig University, Freiburg

Dr Francois Cornelis, genetics of rheumatoid arthritis, GenHotel, University of Evry, France

Prof Markus Löffler, quantitative evaluation of SNP arrays, Institute of Medical Informatics, Statistics and Epidemiology

Prof Peter F. Stadler, genome-wide SNP analyses, Department of Bioinformatics, University of Leipzig

Quality control of mRNA using gel electrophoresis



Project Funding

- The projects receive funding from both the public sector and industry
- Funding for special diagnostics for individualized medicine as an internal program

Competencies

- Animal models (collagen-, adjuvant-, and antigen-induced arthritis)
- Animal experimental models complying with GLP
- Molecular genetics, genotyping, gene expression measurements
- Localization and quantification of human cells in murine tissues using I-FISH
- Karyotype analyses for cells of various origin (classical and molecular cytogenetics)
- Peptide profile analyses in bodily fluids and tissue material
- Designing and conducting genotype-phenotype association studies
- Quantitative measurement of allele-specific gene expression
- Cell culture: cartilage destruction, immunomodulation

Analysis: immunohistochemistry, immunoassays, flow cytometry, fluorescence microscopy, bioassays, multiplex-PCR

Equipment

Genotyping and peptidomics:
- Genolink-System (Bruker Daltonik) comprising thermocyclers, pipetting robot, MALDI-TOF mass spectrometer, software suite; available in cooperation

Cytogenetics:
- ISIS System (MetaSystems) for multicolor FISH; available in cooperation

Molecular cytogenetics:
- System for processing and evaluating Affymetrix GeneChips and human mapping array sets; available in cooperation

Animal Facility:
- TPF

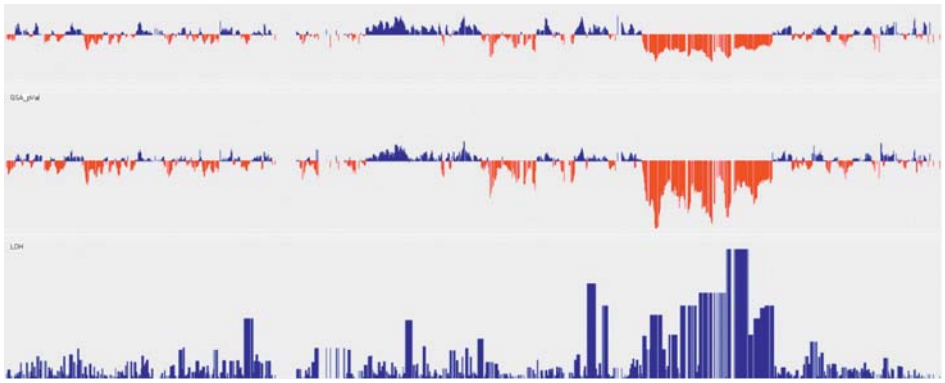
Cell culture and analysis:
- Incubators for cell culture under normoxia and hypoxia, flow cytometer, fluorescence microscope

Imaging:
- Confocal laser scanning microscope, electron microscope, MRT, PET, CT available in cooperation

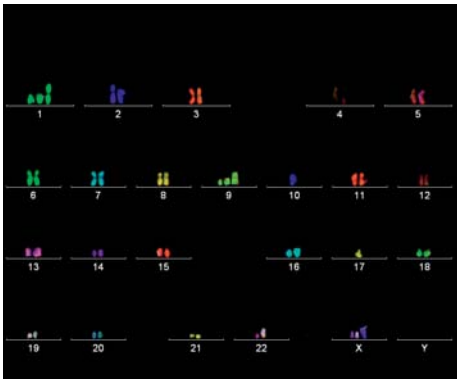
Products and Services

- Analysis of individual response to active agents and drugs (pharmacogenomics)
- Proof of concept of active agents in accordance with GLP rules (animal models for arthritis and tumors)
- Localization and quantification of human cells in mouse tissues
- Karyotype analyses of cells for quality control of (therapeutic) cell material
- Peptide profile analyses e.g. for tumor staging (cells) and transplant rejection (urine)
- Quantitative measurement of allele-specific gene expression for the preparation of gene therapies
- Quantitative determination of oligonucleotides in bodily fluids for therapy monitoring (pharmacokinetics)
- Arthritis models in the mouse including multimodal evaluation (freely combinable) for therapy development (cells or active agents)
- Adaptation of models to other clinical syndromes
- Cell culture model of cellular interaction in arthritis
- Multimodal cell analysis and differentiation

SNP-Array of the Affymetrix Mapping 100K set, 'Copy Number Analysis'



M-FISH karyogram of an esthesioneuroblastoma



Milestones

Pedigree

In the 1920s and 1930s, the Leipzig region became one of the world's most advanced centres of the cutting edge chemical industry. Although the city was unable to take full advantage of its heritage during the East German era, interestingly Leipzig was still chosen to site the 600-strong Central Institute of Biotechnology, which was set up to cope with the emerging field of biotechnological research. IZI is now extending this tradition of biotech.

Continuing and Higher Education Access

Employees in the Leipzig region enjoy a high standard of education and training thanks to prestigious centres of higher education such as the University of Leipzig with 27,000 students, the Leipzig University of Applied Sciences, and the tuition-required Graduate School of Management, which was re-established following German reunification. In fact engineers and technicians account for 14% of the local workforce, while 16% of employees have a college degree.

University of Leipzig

The University of Leipzig was established in 1409, making it one of the oldest centres of academic research in Germany. Following the launch of new departments and the arrival of many relatively young lecturers and professors after 1989, the university enjoyed a renaissance, as reflected by the growing number of externally funded projects. In 2009, the University of Leipzig will celebrate its 600th anniversary by opening a new campus in the city centre, one key element of which will be the Auditorium Maximum.

IZI is a powerful partner for the University of Leipzig in research cooperation and the development of joint teaching and training courses, which make Leipzig an even more attractive location. Ties with the Institute of Clinical Immunology and Transfusion Medicine enable integration into the Faculty of Medicine along with access to departments and medical institutes – and hence to both patients and sample material. Contact with the Faculty of Veterinarian Medicine is also of particular interest, as there are only five such faculties throughout Germany. Having the Faculty of Veterinarian Medicine on the doorstep is an enormous strategic advantage for the future development of IZI, especially given the primarily biosystematic areas of research dealt with by IZI and the numerous analogies between veterinarian and human medicine.

To provide a suitable framework for cooperation, an agreement was signed between the Fraunhofer Society and the University of Leipzig regulating the establishment of endowed chairs, collaboration in research and teaching, the reciprocal attendance of lectures and seminars, and the mutual use of resources.

Translation Centre for Regenerative Medicine

After preparations lasting a number of years, in 2006 the University of Leipzig was granted special funding by the German Ministry of Education

and Research and the Free State of Saxony for the Translation Centre for Regenerative Medicine (TRM). Headed by Prof Emmrich, it is being set up to carry out conceptual, preclinical and clinical research projects in the fields of Tissue Engineering and Materials Sciences (TEMAT), Cell Therapies for Repair and Replacement (CELLT), Regulatory Molecules and Delivery Systems (REMOD), and the Imaging, Modelling and Monitoring of Regeneration (IMONIT). The initial funding amounts to € 20 million over four years. In addition, the Free State of Saxony will make € 17 million available for renovation and equipment. As well as playing a key role in the application to establish TRM, IZI also maintains diverse links with the TRM.

Leipzig Interdisciplinary Centre for Clinical Research

The Interdisciplinary Centre for Clinical Research (IZKF) was founded in 1996 at the Faculty of Medicine to initially focus on cell–cell and cell–matrix interactions of diagnostic and therapeutic significance. So far, the German Ministry of Education and Research has opened nine such centres of excellence following bids from 27 medical faculties. The Leipzig IZKF was the first in eastern Germany – and for some time the only one. Set up by Prof Emmrich, it is now headed by neurobiologist Prof Arendt and concentrates on immunology, endocrinology, the neurosciences and oncology. Apart from more than 25 research projects, the centre also maintains various junior groups and the service units specializing in DNA sequencing and peptide technology. One junior group is devoted to stem cell biology (Dr M. Cross). ORMA (the East German Reference Centre for Micro-array Analysis), where gene expression analysis using the high-density micro-array technique is conducted on behalf of more than 25 partner laboratories, was also set up at Leipzig IZKF.

Biotechnology–Biomedicine Centre (BBZ)

One declared scientific priority of the University of Leipzig is medical biotechnology with particular specialization in molecular development and tissue engineering. Under the Saxony Biotechnology Initiative, five faculties have been established at the Biotechnology–Biomedicine Centre at BioCity Leipzig as a key project with 200 million in funding from the government of the Free State of Saxony. BBZ is headed by Prof A. Robitzki, previously a department head at the Fraunhofer Institute for Biomedical Engineering. Particular support for IZI is to be expected from the departments of Cell Techniques and Applied Stem Cell Biology (Prof A. Bader), Bioprocess Engineering (Prof A. Robitzki), Protein Structure Analysis (Prof. R. Hoffmann), Mass Spectroscopy (Prof N. Sträter), Molecular Cell Therapy (Prof P. Seibel) and Molecular Pathogenesis (Prof M. Blessing).

Clinical Expertise

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

Coordination Centre for Clinical Trials

Innovative structures for clinical research (i.e. planning and performing clinical trials) have become very successfully established in Leipzig. The German Ministry of Education and Research provided funding for the Coordination Centre for Clinical Trials (KKSL) where trial assistants and doctors can be trained and clinical studies devised. In addition, Innomed Leipzig GmbH's Centre for Therapy Studies (ZET) is an organization which carries out clinical trials (mainly high-quality Phase III registration trials) involving doctors treating out patients. Both institutions already work very closely together with IZI.

Interdisciplinary Centre for Bioinformatics

Thanks to financial support from the German Research Foundation, Leipzig has set up an Interdisciplinary Centre for Bioinformatics (IZBI). Its main tasks are the modelling of mechanisms of cellular signal transduction and data processing for cell analysis techniques. In particular, IZI's RNomics Group cooperates intensively with IZBI through Prof F. Horn und Prof P. Stadler.

Interdisciplinary Transgenesis Centre

The Faculty of Veterinarian Medicine (Prof Blessing), the Faculty of Medicine (Prof Schöneberg) and the Max Planck Institute for Evolutionary Anthropology (Prof Pääbo) have joined forces to found a transgenesis centre where pioneering techniques for the introduction and elimination of genes can be developed – for instance in connection with the development of new types of pathogenetic models in animal experiments. The Interdisciplinary Transgenesis Centre is directly adjacent to IZI.

Graduate School of Management

The tuition-requiring Leipzig Graduate School of Management (HHL) has proven to be an outstanding cooperation partner. A number of projects have been conducted in which medics and other scientists have teamed up with business management students and junior lecturers in project teams to compile business plans and marketing strategies. The main person organizing this collaboration is Prof B. Schwetzler from the Department of Business Management – and the success of this approach is demonstrated by the large number of prizes won in business plan competitions. HHL also has a Department of Entrepreneurship running an MBA module for medics and scientists that can be taken alongside medical and science degrees. Many of HHL's students come from abroad and it enjoys a high international reputation. Cooperation with IZI in the field of further training is in the pipeline.

University of Applied Sciences

The University of Applied Sciences (HTWK) dates back to 1764. The largest institution of its kind in Saxony, it currently has more than 6,000 students on 30 courses in the fields of engineering, economics, media and information courses, computer science, mathematics and science. With teaching being closely geared to practical requirements, HTWK's seven departments conduct R&D cooperation with commercial companies and local authority organizations in the region. HTWK's Research and Transfer Centre facilitates the translation of scientific findings into practice. HTWK is creating a new chair in cooperation with IZI, and Prof Emmrich is on the appointment committee.

Max Planck Institutes

Cooperation with the three Max Planck Institutes in Leipzig is only natural. The Max Planck Institute for Human Cognitive and Brain Sciences concentrates expertise in modern imaging techniques and contains the necessary, very expensive facilities needed for techniques such as magnetic resonance tomography. The Max Planck Institute for Mathematics in the Sciences is the other organization behind IZBI alongside the University of Leipzig. Collaboration is especially fruitful with the Max Planck Institute for Evolutionary Anthropology (Prof S. Pääbo), where internationally acclaimed research into molecular and development biology is conducted. It has for example important genomic libraries available. IZI's RNomics team is to be housed there until IZI's new building has been completed.

Centre for Environmental Research Leipzig–Halle

The Centre for Environmental Research Leipzig–Halle (UFZ) is a member of the Helmholtz Association and one of the German's government's biggest research centres. It contains a number of very experienced teams working with bioreactors in the fields of microbiology, sensory technology and cell cultivation. The Department of Environmental Immunology (Dr Lehmann) works in conjunction with IZI to develop cellular detection methods for pollutants that impair the immune systems.

Transport Infrastructure

Leipzig is located on one of the country's main motorway intersections where the A9 (Munich–Berlin) crosses the A14 (Dresden–Hanover). Leipzig/Halle Airport to the north-west of the city operates 24 hours a day and includes intercontinental and cargo services. It was recently chosen by DHL to be its European air freight hub, eventually creating some 10,000 new jobs with DHL and its subcontractors. This outstanding transport infrastructure is augmented by one of the country's six main railway junctions and what has been acclaimed as Europe's most magnificent railway station, connecting Leipzig to Berlin in just one hour. This ensures that in addition to IZI's partners and clients being able to reach Leipzig quickly and conveniently, urgent deliveries of sensitive cells and tissues can be quickly organized by rail, road or air.

Telecom and Media

Leipzig has evolved into an important centre of telecom and media thanks to the presence of one of the world's most advanced glass-fibre networks, Deutsche Telekom's main telecom node in eastern Germany, and the complex of studios and production facilities known as media city are directly adjacent to the television centre of regional broadcaster MDR. Consequently, many businesses in the communications industry often conduct pilot projects and field trials in Leipzig. The city is also famous as a centre of publishing and printing, especially in art, and is home to the prestigious Academy of Visual Arts.

Arts and Leisure

Obsolete open-pit mines south of Leipzig are now being flooded to create one of the biggest lake districts in Germany in a scheme partly funded by the European Union. Some of these lakes are already completed and have become popular for sailing, windsurfing and swimming.

Leipzig city centre contains some world-famous musical ensembles such as St Thomas' Boys Choir and the Gewandhaus Orchestra. In addition to its thriving arts scene, Leipzig is also known as a major sports centre, hosting for example five soccer matches during the 2006 World Cup at its recently completed central stadium. Central Leipzig also has a great network of cycle paths, and the city's general attractiveness is demonstrated by its positive demographics.

New Biotech Companies

The area in and around Leipzig is very conducive for buying land for private purposes and industrial investment. A surplus of newly built buildings and superbly refurbished old building stock makes for inexpensive rents right across the board.

Industrial investment is attracted to Leipzig by factors such as the first-rate infrastructure combined with its high quality of life. Two of the biggest investors in Leipzig in recent years are car-manufacturers Porsche and BMW along with a string of their suppliers.

The local authorities in Leipzig have a well-deserved reputation among investors for their professional assistance coupled with a helpful, unbureaucratic attitude. Manufacturing approval for cell and tissue products throughout the Free State of Saxony is centralized in Leipzig Regional Administration Office.

The disused Leipzig Fair complex in south-east Leipzig offers particularly suitable premises to biotech firms owing to the proximity of many university and non-university research centres along with its excellent transport links. After German reunification, the Leipzig Fair moved to a brand new exhibition centre also containing the Congress Center Leipzig, which has become a magnet for trade visitors and other experts. In 2007 for example, CCL will host the 3rd World Congress on Regenerative Medicine, which is being largely organized by Prof Emmrich and IZI.

The € 100 million BioCity complex was built on the edge of the Leipzig Fair's former exhibition site with funding from both the Free State of Saxony and Leipzig City Council. Housing the University of Leipzig's Biotechnology–Biomedicine Centre (BBZ), it also has 20,000 sqm of space for industrial projects – most of which has already been taken up by more than 25 commercial tenants. They include cell technology companies such as VITA34, International Haemabank, Curacyte and Neuroprogen. BioCity is located on Deutscher Platz just opposite the German National Library and next door to the Max Planck Institute for Evolutionary Anthropology. Other neighbours include the institutes and departments of the Faculty of Veterinarian Medicine. Just a few minutes away are the faculties of medicine, chemistry and physics, as well as biosciences, pharmacy and psychology. BioCity is only ten minutes away from the city centre by car, and can also be easily reached by tram, bus and rail.

Leipzig City Council has reserved a number of sites around BioCity (including on the old exhibition centre) for business start-ups and relocation projects. IZI was able to get off the ground in this attractive scientific and business environment by renting a wing of BioCity. As well as being able to use the conference rooms and canteens, members also take advantage of the events organized by Bionet GmbH, which is responsible for marketing BioCity and is establishing Leipzig as a major centre in the healthcare sector. IZI's new building is currently being erected adjacent to BioCity and is due to be completed by spring 2008.

1 BioCity

2 Faculty of Veterinarian Medicine
including its institutes and departments

3 Max Planck Institute
for Evolutionary Anthropology

4 German National Library

5 Translation Centre
for Regenerative Medicine

6 The site of IZI's new premises

View of BioCity along with the Max Planck Institute
or Evolutionary Anthropology next door

Development of IZI

Background

IZI was founded in 2005 following a resolution passed by the Senate of the Fraunhofer Society. During its development phase, it is receiving support from both the government of the Free State of Saxony and the Innovation and Technology Fund of the city of Leipzig. It was unanimously agreed on by first the specialist committees and finally the Senate of the Fraunhofer Society that IZI would focus on cell therapy and immunology. The German Ministry of Education and Research has provided considerable assistance to IZI.

Management

The structure and operation of IZI are based on the successful experience of other Fraunhofer Institutes gathered over the years. The director of IZI is Prof 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 2006. This dual position enables the efficient sharing of experience, not to mention the optimum supervision of undergraduate and doctoral dissertations, and provides an excellent basis for cooperation. Both a doctor and an immunologist, Prof Emmrich spent 13 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.

Advisory Board

The external Advisory Board is an invaluable source of evaluation and consulting for the management of IZI regarding strategic issues. The members are invited and appointed by the President of the Fraunhofer Society to advise not just the management of IZI but also the Fraunhofer Society's Executive Board in order to optimize the development of IZI. The Advisory Board comprises representatives of industry and research as well as public authorities, government ministries and funding organizations. It meets once a year to discuss IZI's annual report with the Executive Board of the Fraunhofer Society.

Administration

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

Structure

In its current phase of development, IZI is divided into twelve groups managed by their group heads as business units. Their budgets are negotiated with the management of IZI 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.

Run-up to the Foundation of IZI

2002	Development and coordination of the IZI concept
Oct 1, 2003	Concept approved by Life Sciences Alliance
Mar 11, 2003	Concept approved by Main Committee of the Fraunhofer Society
Apr 10, 2003	Senate passes resolution to set up IZI
May 2003	German Ministry of Education and Research confirms support
Oct 2003	Coordination with advisory board of the Leipzig Technology and Innovation Foundation
Nov 4, 2003	Resolution to establish IZI passed by the cabinet of the Free State of Saxony
Nov 2004	Final liaison between national government and the Free State of Saxony regarding the funding of the development phase
Apr 29, 2005	IZI is founded in Leipzig on European Immunology Day

Project Service Team

The concept behind IZI provides for partners and clients to start benefiting from professional project preparation, rapid, flexible contracts, and punctual results even during the development phase. In order to support the groups in their work, a Business Development Team or Project Service Team was set up. Headed by Dr Wilhelm Gerdes, the core of the team consists of three experienced PhD level biologists with additional experience of business development from industry. They are supported by technical assistance in the fields of communication and research as well as with secretarial staff.

The Business Development Team maintains contact with clients and partners, represents IZI at exhibitions and conventions in Germany and abroad, and also prepares the acquisition of contract assignments and projects for the individual groups. Above all, however, the team supports the groups in applying for funding, identifying and serving research consortia, and in their contract negotiations with clients. Moreover, it handles public relations work, reporting and content controlling for projects.

Partnerships

In its current development phase, IZI is particularly dependent on good ties and networking with partner institutions at the University of Leipzig and other non-university research organizations. This enables access to specialist laboratories such as S3 and isotope labs, to imaging techniques with sophisticated equipment, and to facilities for both small and large animals. Over the next few years, IZI will acquire its own animal experiment laboratories as well as special treatment and diagnosis units.

Buildings

Following the establishment of IZI in early summer 2005, the interim facilities for the institute's development were equipped following a careful planning stage. At the same time, steps were taken to ensure IZI would be able to move into its new building as soon as possible. For the time being, a lease was taken out on 1,500 square metres of laboratory and office space in a wing of BioCity on Deutscher Platz in Leipzig. Thanks to intensive support from Leipziger Gewerbehof Gesellschaft, the company headed by Matthias Jähnig which owns and operates BioCity, along with the Fraunhofer Society's construction department, the laboratories were completed by autumn 2005. This is all the more impressive considering that beforehand merely the outer walls were in place, meaning all the normal interior work and mechanical systems had to be completed before the laboratory fittings could be installed.

Prior to to the arrival of IZI, there were no other Fraunhofer institutes in Leipzig. The local authorities demonstrated their commitment by making a prime site available on Zwickauer Strasse in south-east Leipzig not far from the city centre with good transport links on the edge of the old complex of the Leipzig Trade Fair. IZI's new building will be ready in 2008 – and is right next door to the BBZ Biotechnology–Biomedicine Centre containing BioCity for university research and which is also home to 25 biotech companies working in close quarters.

Milestones in IZI's history

Apr 29, 2005	IZI is founded
Oct 2005	First laboratories at BioCity
May 18–19, 2006	Participation in University of Leipzig's 1st Biotech Day
Jun 2006	GMP facility opened
Jun 19, 2006	Saxon Premier Prof Georg Milbradt visits IZI
Jul 12, 2006	IZI's first strategy meeting
Jul 17, 2006	Fraunhofer Society founds Centre for Central and Eastern Europe in Leipzig
Sep 3, 2006	IZI hosts open day
Sep 22, 2006	Foundation stone laid for first wing of IZI's new building; visit by Saxon Minister of Science and Art Dr Eva-Maria Stange
Oct 1, 2006	Translation Centre for Regenerative Medicine founded
Oct 22–24, 2006	Fraunhofer Life Science Symposium
Dec 15, 2006	Participation in 5th University Research Festival

Facilities

On the premises and laboratory space currently used, IZI maintains standard laboratory facilities for biochemistry, molecular biology and cell biology, including a large stock of equippment which is augmented by the systems and instruments used cooperatively. For more details, please see the descriptions of the individual groups.

GMP Facility

One outstanding achievement in terms of precision and speed is the planning and completion of IZI's multipurpose GMP facility at BioCity. 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.

Animal Experiments

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

What's Special about IZI

IZI is a somewhat unusual Fraunhofer institute in one respect. Instead of evolving in small stages from a project group, it is being set up in more or less one go, the aim being to achieve the technology density, quality and revenue of a regular Fraunhofer institute in a short space of time. On the one hand this is a particular compliment for the promising conception and its dynamic development team; on the other, however, this rapid growth harbours a particular responsibility regarding structure and personnel, not to mention the careful use of resources and above all project acquisition under the Fraunhofer system. Ensuring a successful launch was crucial to IZI's workforce and management. All those involved have a sense of pride about what has been achieved – and rightly so.

Foundation of IZI

The youngest child of the Fraunhofer Society was born in Leipzig on 29 April 2005, European Immunology Day. Named the Fraunhofer Institute for Cell Therapy and Immunology, it is more commonly referred to by its German abbreviation IZI.

"Today we've moved a step closer to the goal of turning Leipzig and the surrounding region into an outstanding centre for high level international research," declared Wolfgang Tiefensee, the Mayor of Leipzig, before the some 200 guests in BioCity's glass foyer. Prof Frank Emmrich, the founder and head of IZI, vividly explained some of the scientific themes the institute's groups would be tackling. As an example, he quoted the ability of the salamander to be able to grow a new leg after losing an existing one. "Understanding this process would be a big step forward for medicine."

Alfred Gossner, the CFO of the Fraunhofer Society, reported on the strategic aims of the organization and stated how delighted he was about the growing magnitude and the scientific and commercial success of the Life Sciences Alliance, to which IZI belongs.

Left to right: Dr Frank Schmidt (Permanent Secretary at the Ministry of Science and Art), Dr Alfred Gossner (CFO of the Fraunhofer Society), Wolfgang Tiefensee (Mayor of Leipzig) and Prof Frank Emmrich (head of IZI) at the ceremony to mark the foundation of IZI on April 29, 2005 at BioCity

Dr Alfred Gossner (CFO of the Fraunhofer Society) during his address

Foundation Stone Ceremony

Finally, on September 22, 2006, a Friday afternoon in late summer, it was time for the ceremony to lay the foundation stone for IZI's new home. Ever since IZI had been founded in spring 2005, the staff had been working in premises leased from BioCity – but this would all change when the new building was completed in 2008. Containing 1,600 square metres of laboratories, 1,600 square metres of office space and 450 square metres of GMP laboratories, a total of about 200 people will work there.

The costs of the four-storey building (including initial fixtures, fittings and furnishings) will total €24.6 million. The European Union is funding 60%, the remainder being shared equally between the Free State of Saxony and the German Ministry of Education and Research. The site has been kindly made available free of charge by the City of Leipzig in the form of a hereditary leasehold.

"With Leipzig already a centre of science, the new building will provide a new addition in the field of regenerative medicine," declared Prof Frank Emmrich, the director of IZI, to the some 200 staff and invited guests.

Congratulations were voiced by Dr Alfred Gossner (CFO of the

Left to right: Prof Martin Schlegel (Deputy Vice-Chancellor of the University of Leipzig), Dr Peter Lange (German Ministry of Education and Research) Dr Eva-Maria Stange (Saxon Minister of Science and Art), Dr Alfred Gossner (CFO of the Fraunhofer Society), Andreas Müller (Deputy Mayor of General Administration of Leipzig), Prof Frank Emmrich (director of IZI)

Dr Ekkehard Warmuth from the German Ministry of Education and Research at the foundation stone ceremony for IZI's new building

Fraunhofer Society), Dr Peter Lange (a department head at the German Ministry of Education and Research) and Prof Martin Schlegel (Deputy Vice-Chancellor of the University of Leipzig). The City of Leipzig was represented by Andreas Müller, the Deputy Mayor of General Administration, while Winfried Schmidbauer, an architect from the Stuttgart-based firm of architects Heinle, Wische & Partner also expressed his hopes that construction would proceed "without any accidents or bankruptcies!" Finally, performing her first public official duty in her new role, the newly appointed Saxon Minister of Science and Art Dr Eva-Maria Stange ushered in the start of building work with an address and a trowel of mortar.

Beforehand, site manager Kay Alert and the Business Development Team headed by Dr Wilhelm Gerdes had meticulously prepared the ceremony. For example, in addition to a copy of the day's newspaper, a lock of hair with roots from each employee at IZI was placed in a time capsule. But why exactly? "Well, maybe one day we'll be able to use these hair cells to clone our staff!" explained one of IZI's researchers.

Following the ceremony, bottles of beer were served to all the staff and guests, who drank to the successful start of construction work and inspected the excavations one last time where the foundations were about to be laid.

Newly appointed minister Dr Eva-Maria Stange performing her first official duty at the ceremony

Participants relax during the evening social at Leipzig Zoo's Kiwara Lodge

1st Fraunhofer Life Science Symposium, Leipzig

The 1st Fraunhofer Life Science Symposium was held in Leipzig from 22nd–24th of October 2006. IZI's annual Life Science Symposium makes an important contribution to establishing Leipzig as a centre of the biotech industry. When it was first held, the three-day international congress was attended by 250 representatives from research, medicine and business along with 40 exhibitors from industry. The general theme of the first symposium was regenerative medicine, especially in connection with the development of innovative types of therapy.

The symposium opened on the morning of 23 October with an address by Burkhard Jung, the Mayor of Leipzig. The State Ministry for Economic Affairs and Labour, which partly funded the symposium, was represented by Dr Frank-Peter Schulze.

Internationally renowned groups of scientists used the Life Science Symposium to present and discuss their latest findings in the fields of immune tolerance, cell therapy (neurological, cardiovascular and liver), spinal cord regeneration, imaging techniques and regulatory matters.

The speakers from 13 different countries included Jeff Bulte from the USA, a leading authority on imaging techniques. His paper addressed the MR imaging of stem cells in immunotherapy. Kathryn Wood from

Prof Gerd Hasenfuß presenting a paper on testicular stem cells

the University of Oxford spoke on the balance between innate and adaptive immune responses. Bernd Arnold focused in his paper on peripheral T-cell tolerance in a developing immune system as opposed to an adult immune system. One particularly influential researcher in his field is Piero Anversa, who demonstrated for the first time the existence of stem cell populations in the heart which are evidently able to regenerate coronary arteries.

Johannes Schwarz talked about the role of neuronal stem cells and dopamine precursor cells in the treatment of Parkinson's disease. Eva Syková presented the first clinical results of cell therapy applied to spinal cord regeneration. Karoly Nikolich from Stanford University gave an overview of the principal mechanisms of new types of therapy for diseases of the central nervous system.

In addition to the scientific papers, another key aim of the symposium was to create a dialogue between research and industry on the particular interests and needs of both sides and to encourage the exchange of experience on new therapeutic approaches in the life sciences. Accordingly, several industry representatives took part in the symposium such as Andreas K. Nüssler from the Fresenius Institute, who is widely regarded as an expert in stem cell research, and who differentiates hepatocyte-like cells from stem cells in order to use them for liver regeneration and drugs research.

Meanwhile commercial companies like Novosom and Schering introduced presented ground-breaking technologies in a series of papers entitled 'New Industrial Technology Platforms'. Dr Hermann Graf von Schering for example spoke about the commercialization of therapeutic cell products. The formal part of the symposium was rounded off on October 23 with a cultural highlight – namely an exclusive evening guided tour of Leipzig Zoo followed by African sounds and flavours in one of the zoo's restaurants, the Kiwara Lodge.

Poster exhibition at the 1st Fraunhofer Life Science Symposium

Dr Henryk Barthel talking about new imaging techniques

The visit by the Saxon premier generated high media interest

IZI Visited by Saxon Premier

On 19 June 2006, the prime minister of the Free State of Saxony – Prof Georg Milbradt – visited IZI at BioCity in order to experience for himself its successful launch and to discuss the latest research techniques and findings with the scientists working there. Prof Milbradt was welcomed by IZI director Frank Emmrich, who spoke about the current and future activities of the institute. During the tour, Prof Emmrich showed the Saxon premier the new clean room facility used for the production of clinical trial samples and some of the research work being conducted at IZI.

The government of the Free State of Saxony and the City of Leipzig are both closely involved in supporting the development of IZI.

Dr Andreas Schubert from IZI talking to Prof Georg Milbradt, the prime minister of Saxony

Appearances: Biotechnology Festival at the University of Leipzig

On the 18th and 19th of May 2006, the University of Leipzig's Biotechnology Festival was held. This was the fifth time this important event, had been staged – but the first time it had been spread over two days. Hosted in BioCity on Deutscher Platz, it covered the themes of nanobiotechnology, nanomedicine and bioinstruments. The symposium was established by the Biotechnology–Biomedicine Centre (BBZ) together with three regional research alliances – the German Research Council's Collaborative Research Project 610, ConTecToLife (Connecting Technologies to Life – the Life Sciences Cluster in central Germany), and the Interneuro postgraduate research programme.

New biotech findings were presented in a relaxed scientific atmosphere by more than 200 researchers. An exhibition featuring more than 170 posters (including 18 from IZI) provided an overview of current research. A total of 15 papers were presented under the umbrella title 'From molecule to patient – new key technologies in diagnosis, therapy and therapy monitoring'. In addition, several firms and institutions had set up information stands about the biosciences in the Leipzig region and the latest developments in this budding industry. IZI also had its own display stand manned by the Business Development Team.

Open Doors Day at IZI

On 3 September 2006 an open door day was held at BioCity. IZI of course participated, although IZI has only temporary accommodations at BioCity. An informative stand was set up to explain to visitors of all ages IZI's varied work in the life sciences. For instance diverse types of cells were displayed under advanced microscopes and visitors' questions were answered by experts.

A children's corner was set up where colourful charts and pictures displayed the structure of the human body. This display proved to be very popular and left almost no question from younger visitors unanswered.

In addition to the huge scientific curiosity expressed, the imminent start of construction work on IZI's permanent home next door was also a frequent topic of interest.

Delighted that the event went off so successfully, all those involved from IZI are now eagerly looking forward to the next open door day.

Members of IZI answered visitors' questions on stem cells

Visitors young and old alike were fascinated by this close-up view of cell biology through a modern microscope

TRANSLAT

In a joint research project with the Institute for Clinical Immunology and Transfusion Medicine (IKIT), the Faculty of Medicine of the University of Leipzig, and a Leipzig company, a type of experimental cell therapy for stroke has been developed based on cells from umbilical cord blood and bone marrow. Very promising results enabling transition to clinical trials have already been achieved in both small- and large-animal models.

The aim of the joint project TRANSLAT is to develop selected cell-therapy techniques to the level at which Phase IIa clinical trials can be commenced. In addition to experimental testing, another key aspect of the project is the theoretical preparation of a clinical trial – from drawing up the protocol to obtaining the necessary approval (ethics committee, Paul Ehrlich Institute or EMEA). The Neurorepair Group at IZI is providing important findings for this project from animal experiments. Furthermore, project work will also be assisted by experts in GMP production and GCP from IZI. The project has been supported since 2006 by Saxon development bank Sächsische Aufbaubank (SAB).

Transplantation Tolerance

The German 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 a 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 like this can be used to test strategies that can then be transferred to common use.

Cooperation with Indonesia

In 2006, IZI conducted a preparatory study on establishing new types of cell-based treatment in Indonesia. The main aim was to evaluate the scientific and technical possibilities of conducting clinical trials in the domain of regenerative medicine.

Dr Ida-Bagus Kesawa Narayana, the Fraunhofer Society's representative in Indonesia, acted as liaison to put IZI in contact with the Indonesian partner companies. Moreover, Dr Johannes Boltze, the head of IZI's Neurorepair Group, and Dr Christian Zilch from the Project Service Team gave a number of talks at universities, research centres and mid-sized firms. They finished off their journey with two days spent in Singapore to discuss areas of possible cooperation with industry and university partners. So far, this project has been solely funded internally by the Fraunhofer Society.

Stem Cell Biology/Stem Cell Technology

The German 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 mankind's 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 ageing 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 drugs testing.

Cooperation

Introduction

Interdisciplinary cooperation is essential for IZI if it is to perform its scientific mission. Internal and external scientific cooperation, further training and teaching as well as active involvement on specialist committees enable the necessary exchange and secure and increase competitiveness for future projects. Within the Fraunhofer Society we are able to use the competencies of institutes and hence develop system solutions. IZI's members of staff are prepared to deal with the developments of dynamic markets and future partnerships on internal and external training courses. Meanwhile the close cooperation and personal ties of IZI with the University of Leipzig are a valuable source of stimulation and provide direct access to the practical clinical experience. Examples of cooperation projects at IZI are outlined on the following pages.

Research Cooperation

Remedy

Remedy (Regenerative Medicine – Support Networks in Tissue Engineering Innovation Systems) is an innovation project set up by the European Union to identify obstacles to innovation besetting start-ups and medium-sized companies in Europe. In this cooperation, tailored support measures in the field of tissue engineering are being developed in regional and European networks. Given the extremely dynamic nature of research in this field, it is vital that the pertinent legal, commercial, technological and not least ethical conditions be properly drafted and unified. And together with other associations and scientists, IZI is playing its part. In autumn 2005, Dr Sonya Faber from the Business Development Team gave talks in Estonia about new European legislation affecting tissue engineering. The aim is to introduce uniform standards for the approval of tissue engineering products and to develop joint training programmes for the scientific and technical personnel involved.

Tissue Factory

As a member of the Fraunhofer Life Sciences Alliance, IZI is taking part in an internal call for projects for the sustainable development of new competencies in the field of tissue cultivation. Apart from the Life Sciences Alliance, the Fraunhofer Society's Production Alliance is also involved in this innovative project, which is designed to provide new research techniques eventually resulting in a 'tissue factory'.

The enormous potential for innovation harboured by tissue engineering can only be harnessed by means of an integrated methodology comprising both a thorough understanding of the processes taking place in cell biology and the optimization of the way in which tissue engineering products are made – and which also meets the high standards governing the handling of biomaterials in terms of quality and reliability. It was for this reason that the Life Sciences and Products alliances have teamed up to start a joint project.

Nano-4-Nerves – Czech–German Partnership

Nano-4-Nerves, a Czech–German project, is being planned in cooperation with the Jülich Research Centre. The two project heads are Prof Eva Syková from the Czech Academy of Sciences and Prof Emmrich representing IZI and the Fraunhofer Society. The aim of cooperation is to jointly develop pioneering methods of cell therapy treatment for ischaemic and traumatic neuronal diseases, stroke and paraplegia. The project outline calls for the simultaneous involvement of both partners over a period of five years. One important aspect is the transfer of knowledge between the two countries. The proximity of Prague and Leipzig at the heart of Europe ensures not only the swift flow of information but also possibilities for bilateral personnel training. A preparatory and feasibility study for the project has been scheduled to start in 2007 and is financed by the German and Czech research ministries. The project has been given the go-ahead, and a full application will be submitted in December 2007.

Invest in Germany

Invest in Germany is an official German investment promotion agency set up by the German Ministry of Economic Affairs and Technology. Its mission mainly comprises representing Germany as a centre and partner for international business as well as distributing information and market analyses on specific sectors.

In June 2006, IZI's Business Development Team took part in a one-week road show through Canada and Texas organized by Invest in Germany. Designed to highlight and pave the way for possible investments in the field of innovative technologies Germany, others participating in the road show included Jörg Menno Harms (chairman of Hewlett-Packard GmbH's supervisory board) and Dirk Hilbert, the Mayor of Dresden.

INVEST IN GERMANY

Biotechniques – Models

University of Salzburg, Austria, Immunotoxicology

Helmholtz Centre for Environmental Research, Leipzig, Department of Environmental Immunology, Department of Cell Toxicology, Department of Proteomics, Immunotoxicology

Polish Academy of Sciences, Lodz, Centre for Molecular and Macromolecular Studies, Prof Stanislaw Slomkowski, Poland, Nanotoxicology

Czech Academy of Sciences, Institute for Macromolecular Chemistry, Prague, Czech Republic, Immunotoxicology

Fraunhofer Institute for Applied Polymer Research (IAP), Department of Water-Based Polymer Systems, Potsdam-Golm, Immunotoxicology

Jean Pierre Aubert Lille Centre, Lille, France, Immunotoxicology, Neurotoxicology

University of Leipzig, Paul Flechsig Institute for Brain Research, Leipzig, Immunotoxicology, Neurotoxicology

Christian Albrecht University, Kiel, Anatomical Institute, Immunotoxicology, Neurotoxicology

University of Leipzig, BBZ Biotechnology-Biomedicine Centre, Cell Technology and Applied Stem Cell Biology, adaptation of GLP standard conditions for autologous MSC transplantation

University of Leipzig, BBZ Biotechnology-Biomedicine Centre, Institute for Bioanalytics, biomarkers, defensines

University Hospital Leipzig, Department of Intensive Medicine, defensines

University of Leipzig, Faculty of Veterinarian Medicine, Institute for Immunology, defensines

Immunology – Immunomodulation

Fraunhofer Centre for Central and Eastern Europe, Leipzig, HIV infection in Europe

University of Leipzig, Institute for Virology, measles (including German measles)

University of Leipzig, Institute for Clinical Immunology and Transfusion Medicine, HIV infections in Europe; tolerance induction

National Cancer Institute, HIV Drug Resistance Program, Frederick, USA, HIV restriction

SAIC, AIDS Vaccine Program, Frederick, USA, Cell Hybrids National Cancer Institute, Center for Cancer Research, Frederick, USA, NK cells

University of Oxford, UK, infectious synapse

Helmholtz Centre for Infection Research, Brunswick, glycobiology

Martin Luther University, Halle–Wittenberg, Institute for Biotechnology, Institute for Pharmacy, Halle, DC-SIGN structure

Ludwig Maximilian University, Munich, Institute for Molecular Immunology, immunological synapse

University of Dortmund, Department of Chemistry, HIV evolution

Vanderbilt University, Nashville, TN, USA, lentiviral vectors

University of Leipzig, BBZ Biotechnology-Biomedicine Centre, Institute for Bioanalytical Chemistry (in foundation), antimicrobial components

University of Leipzig, Institute for Organic Chemistry, DC-SIGN structure

University of Leipzig, Department of Biochemistry, DC-SIGN structure

University of Leipzig, Translation Centre for Regenerative Medicine, cultivation of human CD4+ cells and murine CD4 cells, human DR+ mouse stem

University of Leipzig, Medical-Experimental Centre, localization to perform transplants on small rodents, animal husbandry, sterile departments

University of Leipzig, Medical Department II (haematology/ oncology), Leipzig, diagnostic strategies of graft-versus-host-disease (GvHD) in humans

University of Leipzig, Department of Radiation Therapy, performance of radiation treatment as part of conditioning treatment

Charité, Benjamin Franklin Campus, Medical Department III, Berlin, scientific cooperation in the establishment of GVHD models and diagnostics of GVHD in animal models

University of Leipzig, Institute for Clinical Immunology and Transfusion Medicine, performance of analytical methods (e.g. histology, flow cytometry, cytometric bead array)

University of Leipzig, Institute for Medical Microbiology and Epidemiology of Infectious Diseases, scientific cooperation on microbiological challenge tests (in development), real-time PCR

Cell Therapy – Active Agents

University of Leipzig, Faculty of Veterinarian Medicine, large-animal models

University Hospital Leipzig, Radiology Centre, functional imaging

University Hospital Leipzig, Department of Neurology, preparation of clinical trials

University of Cologne, Cologne, reprogramming of stem cells

University of Hohenheim, Stuttgart, impact of oxidative stress on adult stem cells

University of Tübingen, differences between in vitro ageing of adult stem cells and human reproductive stem cells

University of Leipzig, new agonists and antagonists of the hedgehog signal pathway for the differentiation of adult stem cells

University of Hamburg, theories of ageing

University of Sheffield, UK, development of 3-D culture models for the expansion of adult stem cells

Sheffield Hallam University, UK, adult stem cells in diabetes

University of Sheffield, UK, characterization of adult stem cells from SOD mutant mouse

University of Leeds, UK, ageing of human MSC

Arizona State University, Tempe-Arizona, USA, identification of bacterial proteases for regenerative therapy

University of Sheffield, Sheffield, UK, proteomics of human MSC

Federal Institute for Risk Assessment, Berlin, involvement in the development of an osteotoxicity model

Hanover School of Medicine, cooperation partner, embryonic stem cells from Callithrix jacchus

Central Institute for Experimental Animals, Kawasaki, Japan, embryonic stem cells from Callithrix jacchus

Stanford University, San Francisco, CA, USA, murine ES cell line with LEF/TCF-GFP reporter available

Ottawa Health Research Institute, Ottawa, Canada, murine ES cells expressing wnt3a

University of Calgary, Canada, part of the NIH project 'Directed Stem Cell Differentiation for Cell-based Therapies for Aging Diseases'

Merseburg University of Applied Sciences, rapid prototyping

Molecular Biology – Individualized Medicine

Albert Ludwig University, Freiburg, clinical research group for rheumatology, pharmacogenetics

University of Evry, France, pharmacogenetics

University of Leipzig, Institute for Medical Informatics, Statistics and Epidemiology, pharmacogenetics

University of Leipzig, Department of Bioinformatics, genome-wide SNP analyses

University of Leipzig, Translation Centre for Regenerative Medicine, identification of xenogeneic cells

University Hospital Leipzig, Locomotive Disorders Group, identification of xenogeneic cells

Martin Luther University, Halle–Wittenberg, Department of Internal Medicine I, identification of xenogeneic cells

Philipp University, Marburg, Institute for Immunology, quantitative determination of therapeutic nucleotides

University of Montpellier, France, dendritic cells and arthritis

University of Zurich, Switzerland, fibroblasts and SCID mice in arthritis research

University of Jena, experimental arthritides, fibroblasts

Ludwig Maximilian University, Munich, cytokine regulation of arthritides

University of Bochum, lentiviral vectors

University of Lund, Sweden, MTX therapy of arthritides

Humboldt University, Berlin, rheumatoid arthritis

University of Vienna, Austria, gene therapy for arthritides

University of Addis Ababa, Ethiopia, HIV diagnosis

University of Alexandria, Egypt, immunotoxicology

University of Jerusalem, Israel, fibroblast-induced cartilage destruction

University of Leipzig, Interdisciplinary Centre for Bioinformatics, Leipzig, array analysis

University of Leipzig, Interdisciplinary Centre for Clinical Research, Leipzig, array analysis

Max Planck Institute for Evolutionary Anthropology, Leipzig, ncRNA expression in primates (Pongoland, Leipzig Zoo)

University of Leipzig, Institute for Biochemistry, RNA biochemistry

Martin Luther University, Halle–Wittenberg, Institute for Biotechnology, Halle, viral ncRNAs

University of Vienna, Theoretical Biochemistry, Institute for Theoretical Chemistry, Vienna, Austria, RNA bioinformatics

Innsbruck University of Medicine, Austria, RNA knockdown

Universitair Medisch Centrum St Radboud, Nijmegen, Netherlands, diagnostic ncRNAs

Sahlgrenska akademin, Göteborgs Universitet, Department of Urology, Göteborg, Sweden, NcRNAs in the prostate carcinoma

Weizmann Institute for Science, Tel Aviv, Israel, annotation of RNAs

Universidad de Pompeu Fabra, Barcelona, Spain, in silico tumour models

Arizona State University, Phoenix, AZ, USA, transcriptional regulation of ncRNAs

Yale University, New Haven, CT, USA, microRNA expression and evolution

Chinese Academy of Sciences, Max Planck Society Partner Institute for Computational Biology, Shanghai, China, identification of regulatory elements in ncRNA genes

National Institute for Medical Research, London, UK, RIP-chip

European Bioinformatics Institute, Hinxton, UK, tiling array analyses

Charité University of Medicine, Berlin, Institute for Fluid Mechanics, establishment of an in vitro flow model for cardiac valves

Martin Luther University, Halle–Wittenberg, Medical-Experimental Centre, Halle, flow apparatus

University of Leipzig, Faculty of Veterinarian Medicine, endocardiosis in dogs

Department of Conservative Dentistry and Periodontology, Leipzig, provision of patient isolates to test antimicrobial peptides

Friedrich Schiller University, Jena, Department of Preventive Dentistry, provision of standard laboratories to test antimicrobial peptides

Teaching and Training

TSA Ostwald

The Technology Student Association (TSA) is a US organization whose motto is "Learning to live in a technical world". Every year it hosts an international science competition for teams of students and schoolchildren, the final of which is always held in the USA. In connection with this competition, IZI is pleased to lend support to a Leipzig high school. The school students receive assistance from the various scientific groups at IZI during work experience and research seminars, are given plenty of mental stimulation, and discuss possible solutions to life science problems.

Wilhelm Ostwald School in Leipzig, which caters to children who are especially gifted at mathematics and the natural sciences, is the only TSA chapter in Europe. Ever since TSA Ostwald was founded in 2001, the committed school students have successfully presented every single year. For example in 2006 the presentation given by the Cyberspace Pursuit group won first prize.

TSA students at the presentation ceremony in Dallas

Participant Stefan Döge from Wilhelm Ostwald School holding the trophy

BibBio

In 2006, a consortium consisting of IZI and bib-group outplacement GmbH, a private career training organization and service provider, launched a programme to boost the training of female medical-technical assistants to become biotechnology specialists. At present there are 15 participants. The programme receives financial backing from the development bank Sächsische Aufbaubank and will come to an end in 2007.

The aim is to offer participants a complete range of services comprising consulting, further training and coaching. As a result, highly qualified and motivated graduates in various fields of biotechnology will join the employment market. Broad new job opportunities will arise for the participants following the reactivation of their communicative and teamwork skills in combination with the acquisition of technical knowledge and an improvement in their level of English. Practical training at IZI will also help the participants' networking no end by putting them in touch with plenty of small and mid-sized biotech companies and service providers.

The project has a total duration of nine months and is divided into a four-month theoretical phase followed by a five-month practical section. The extensive work experience at IZI enables participants to demonstrate what they have learned – and thus raises their chances of securing employment afterwards.

Teaching activities:

L = lecture
S = seminar
P = practical training
C = course
L = student training and teaching
F = further training
PBL = problem-based learning

IZI staff are intensely involved in teaching and further training

University of Leipzig

Autoimmune diseases	S
Biotechnology	L
Biotechnology/regenerative medicine	L
Clinical immunology	L
Current literature on non-coding RNAs	S
Depiction of damaged organs within the organism as a whole	F
Immunogenetics	L
Immunology – application, clinic, diagnosis	S
Interdisciplinary subject: immunology/infections	C
Introduction to independent scientific work	S
Introductory immunology	S
Laboratory practical: molecular medicine for biochemists	P
Laboratory practical: molecular medicine for biologists	P
Main lecture on immunology (guest lecture)	L
Med bio tech	L
Medical biotechnology for students of medicine	L
Medical biotechnology	L
Medical immunology for dentists	L
Molecular diagnosis	L
Molecular medicine for biochemists	P
PBL: Emergency medicine	T
PBL: Infections and immunology	T
Pharmacogenomics for biochemists	L
Postgraduate training: 'Immunology'	L, P
Practical training in immunology	P
Regenerative medicine for students of medicine	L
Seminars for doctoral students	S
Therapeutic options of stem cells	L
Tutoring 'English in medicine'	T
Vectors in gene therapy	L

IZI

Supervising undergraduate dissertations (6)	T
Supervision doctoral theses (8)	T
Supervising doctoral theses in medicine (8)	T

University of Calgary, Canada

Supervising undergraduate dissertations	T
Graduated with Bachelor of Science (Hns)	T
Graduated with Master's of Science	T

Wilhelm Ostwald School, Leipzig

Tutor BELL Project	T

Lausitz University of Applied Sciences, Senftenberg

Immunogenetics	L

bib-group outplacement GmbH, Leipzig

Methods in microbiology	F
Specialist in biotechnology	F

Internal Career Development

IZI attaches particular importance to further training for its staff. The following further training courses were conducted in 2006:

- Acquisition seminar, June 2006
- Instruction in genetic engineering, September 2006
- GMP/GLP documentation requirements, April 2006
- In-house equipment training: multifunction plate reader, pipette collaboration unit, Beckmann Coulter flow cytometry, LC480 real-time PCR, Äkta Purifier (protein purification), autoclave, liquid nitrogen system, centrifuges and freezing unit
- Internal GLP/GMP training courses (quality assurance), April/May 2006
- Team-building seminar, September 2006

External Career Development

- 3rd Innovation Forum on Presymptomatic Tumour Diagnosis, Dresden
- 17th Workshop for Experimental and Clinical Liver Transplantation and Hepatology, Wilsede
- Applied Biosystems, Berlin, real-time PCR course
- Tumour Immunology and Experimental Stem Cell Transplantation Group, chemotherapy and transplantation for the induction of GvHD in a mouse model, Berlin
- Tumour Immunology and Experimental Stem Cell Transplantation Group, bioluminescence and GvHD diagnosis in a mouse model, Berlin
- Autoimmune disease diagnosis in practice, Dresden
- BD/Invitrogen, flow cytometry/cell separation, Leipzig
- BioMed Concept GmbH, Berlin, further training sessions pursuant to Section 15 Genetic Engineering Safety Regulations
- Career Management Seminar Series, University of Calgary, Canada
- Concept Heidelberg, 'The quality control manager'
- DECHEMA Society for Chemical Engineering and Biotechnology, Frankfurt am Main
- Karlsruhe Research Centre, GLP course, Karlsruhe
- Further training and exchange of experience for assessors, Frankfurt
- Fraunhofer Venture Group Munich, Stuttgart, business plan game
- GE Healthcare Munich, ÄKTA Training
- GE Healthcare Munich, Äkta-Purifier (protein purification)
- GE Healthcare Munich, Proteomics, Leipzig
- GMP Webinar Concept Heidelberg, new pharmaceutical and drugs regulations
- GMP Webinar Concept Heidelberg, GMP in the early phases of development with emphasis on biopharmaceuticals
- Paediatric immunology, rheumatology, environmental medicine, allergology, laboratory medicine, Grimma
- Thermo Electron Leipzig, Proteomics, Leipzig
- University of Leipzig, introductory course on radiation protection for doctors and instruction in radiation protection in X-ray diagnosis, radiation protection for the acquisition of the X-ray proficiency certificate for doctors
- University of Leipzig, MD/PhD degree programme
- University of Leipzig, course on working with laboratory animals
- University of Leipzig, PBL workshop
- University of Leipzig, SMILE seminar on presentation and communication training
- University of Leipzig, SMILE seminar on time management
- University of Leipzig, special course
  - X-ray diagnosis and special course
  - Computed tomography, special course
  - Acquisition of the X-ray proficiency certificate for doctors
- Webinar on new legal requirements for GLP/GMP

Membership of Associations

- Human Genome Variation Society (HGVS)
- Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie (GMDS; German Society for Medical Computer Science, Biometry and Epidemiology)
- American Association for the Advancement of Science
- National Institutes of Health, Immunology Interest Group, USA
- National Institutes of Health, Virology Interest Group, USA
- AG Experimentelle Stammzelltransplantation (Experimental Stem Cell Transplantation Study Group)
- Gesellschaft zur Förderung der Immundiagnostik e.V. (Society for the Promotion of Immunodiagnostics)
- Deutsche Gesellschaft für Immunologie (DGfI; German Immunology Society)
- Gesellschaft für Versuchstierkunde (GV-SOLAS; Society for Laboratory Animal Studies)
- Arbeitskreis Transplantationsimmunologie, Gesellschaft für Immunologie (Transplant Immunology Study Group, Immunology Society)
- Arbeitskreis Durchflusszytometrie und quantitative Mikroskopie, Gesellschaft für Klinische Chemie und Laboratoriumsmedizin (Flow Cytometry and Quantitative Microscopy Study Group, Society for Clinical Chemistry and Laboratory Medicine)
- Gesellschaft für Zytometrie (Cytometry Society)
- Deutscher Hochschulverband (German Association of Universities and Colleges)
- Deutsche Gesellschaft für Gerontologie und Geriatrie (German Gerontology and Geriatric Society)
- Deutsche Gesellschaft für Altersforschung (German Gerontology Society)
- Biochemical Society, UK
- Gesellschaft für Stammzellforschung (Society for Stem Cell Research)
- Society for Developmental Biology
- International Society for Stem Cell Research
- American Society for Cell Biology
- Canadian Society of Biochemistry, Molecular and Cellular Biology

Functions on Specialist Committees

- Advisory member of Deutsches Instituts für Normung (DIN; German Industry Standardization) for Section7, Medical Standards Committee, Interoperability Committee
- Member of the Executive Committee of Verein zur Förderung der Gesundheitswirtschaft in der Region Leipzig e.V. (VFG; Association for the Promotion of the Healthcare Sector in the Leipzig Region)
- Representation of DGfI (German Immunology Society) in Arbeitsgemeinschaft der Medizinisch-Wissenschaftlichen Fachgesellschaften (AMWF; Association of the Scientific Medical Societies in Germany)
- Secretary General of the Association of Clinical Research Centers of German Universities (ACRC)
- Chair of Leipziger Initiative für Biotechnologie e.V. (Leipzig Biotechnology Initiative)
- Chair of Zentrum für Therapiestudien e.V. (Centre for Therapy Trials)
- Management of the Translation Centre for Regenerative Medicine of the University of Leipzig
- Representation of DGfI on GLP Committee, Gesellschaft für Immunologie (Immunology Society)
- Representation of DGfI on Arbeitsgemeinschaft Medizinischer Laborfachgesellschaften, Gesellschaft für Immunologie (Association of Medical Laboratory Companies, Immunology Society)
- Representation of DGfI on Sector Committee 5 of Zentralstelle der Länder für Gesundheitsschutz, Gesellschaft für Immunologie (Central Healthcare Bureau, Immunology Society)
- Coordination of the German Group of European Autoimmunity, Standardization Initiative (EASI; since 2005; Sack, U.)
- Member of the Executive Committee of Gesellschaft zur Förderung der Immundiagnostik (Society for the Promotion of Immunodiagnostics)
- Trainee Advisory Committee, Canadian Stem Cell Network
- Annual General Meeting Steering Committee, Canadian Stem Cell Network
- Board of Directors, Chair Research & Industry Committee, Student Society for Stem Cell Research
- Junior Investigators Committee, International Society for Stem Cell Research

IZI is a member of the following associations:

- Verein zur Förderung der regenerativen Medizin e.V. (Association for the Promotion of Regenerative Medicine; since 2005)
- Verein zur Förderung der Gesundheitswirtschaft in der Region Leipzig e.V. (VFG; Association for the Promotion of the Healthcare Sector in the Leipzig Region; since 2005)
- Deutsche Gesellschaft für Regenerative Medizin e.V. (German Regenerative Medicine Society; since 2005)

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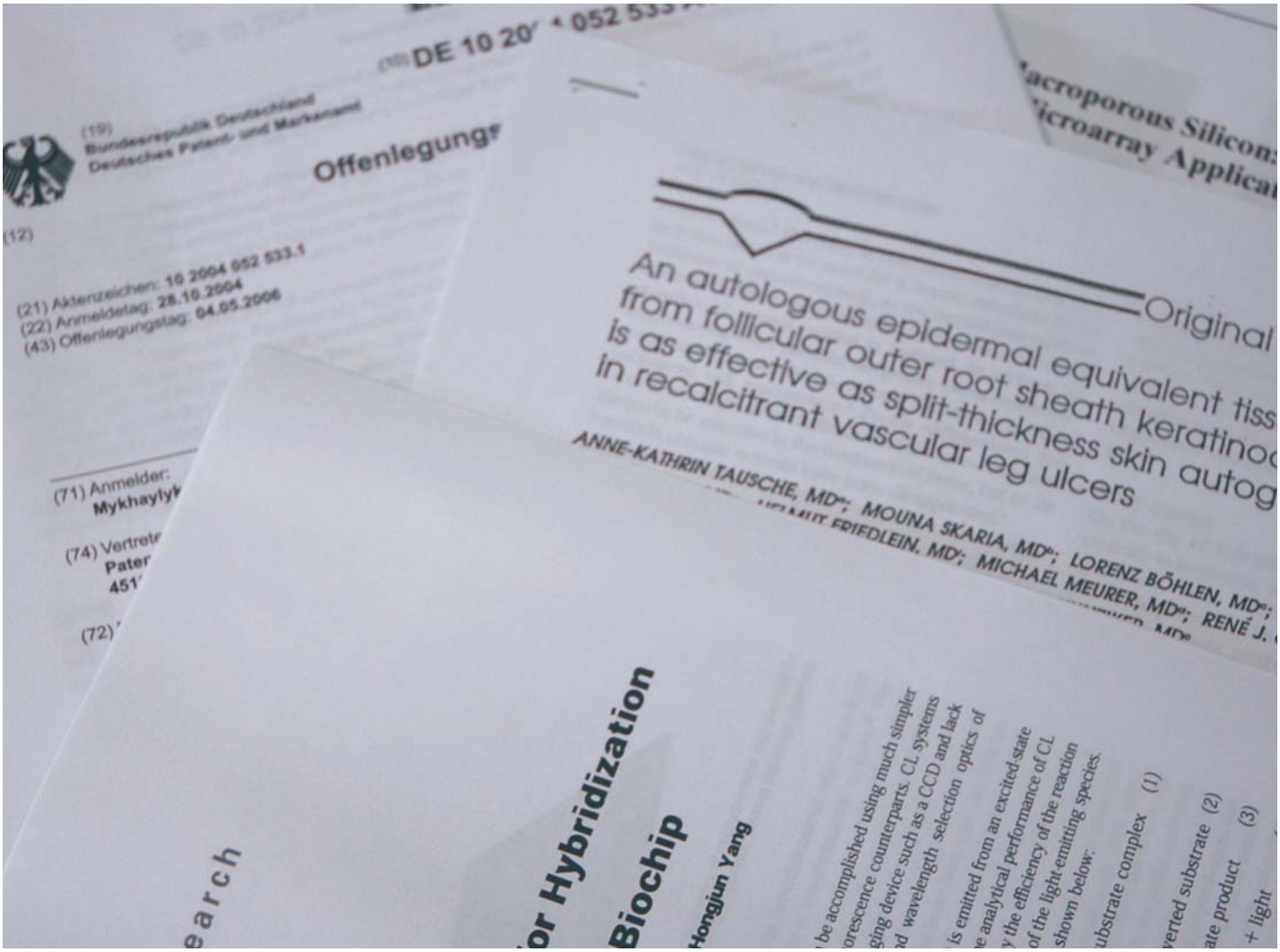

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Papers

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Ahnert, P.
Quantitative and allele-specific measurements of gene expression
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Sack, U.
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Sack, U.
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Sack, U.
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A candidate gene association study using the Genolink system revealed presumptive associations with Rheumatoid arthritis
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Chondrogenic & osteogenic lineage inducers in ES cells
INYS workshop, January 2005, Cambridge, UK

zur Nieden, N.I.
Embryonic stem cells as a model for bone and cartilage development: bioengineering of skeletal tissue
Cell therapy seminar series, University of South Florida, September 2005, Tampa, USA

zur Nieden, N.I.
ES cell differentiation: a story of the skeleton
Tissue Engineering & Regenerative Medicine seminar, Imperial College, January 2005, London, UK

zur Nieden, N.I.; Cormier, J.T.; Kallos, M.S. & Rancourt, D.E.
Billions of stem cells for cytotherapy: Quality controlled expansion in bioreactors
1st Annual Stem Cells and Regenerative Medicine Symposium, January 2006, Burlingame, CA, USA

zur Nieden, N.I.; Cormier, J.T.; Kallos, M.S. & Rancourt, D.E.
Generating billions of stem cells for cell therapy
Current topics in Maternal & Child Health seminar series, University of Calgary, October 2005, Calgary, Canada

zur Nieden, N.I.; Davis, L.A.; Geransar, R.M. & Rancourt, D.E.
Wnt, BMP and nitric oxide signaling converge to regulate betacatenin levels during osteogenic differentiation of embryonic stem cells
Canadian Stem Cell Network 4th Annual General Meeting, November 2005, Calgary, Canada

zur Nieden, N.I.; Liu, S.Y.; Matyas, J.R. & Rancourt, D.E.
Biodegradable calcium-phosphate scaffolds trigger osteogenic differentiation of embryonic stem cells
3rd Annual Canadian Biomaterials Society Meeting, May 2006, Calgary, Canada

Awards, Prizes and Scholarships

Baumann, J. G. & Breun, S.K.J.
NIH Postdoctoral Fellowship
National Cancer Institute, 2000–2005

Boltze, J.
1st poster prize: : MRT der experimentellen fokalen zerebralen Ischämie beim Schaf
87. Deutscher Röntgenkongress 2006, May 2006, Berlin

Koschny, R.; Holland, H.; Sykora, J.; Sprick, M.R.; Haas, T.L.; Ganten, T.M.; Krupp, W.; Bauer, M.; Ahnert, P.; Meixensberger, J. & Walczak, H.
Poster prize: Bortezomib sensitizes primary human esthesioneuroblastoma cells for TRAIL-induced apoptosis
GMS German Medical Science 2006; 27. Deutscher Krebskongress, March 2006, Berlin

Stolzing, A.
Reise-Stipendium: WUN (World University Network)
November 2005

Stolzing, A.
Poster prize: From the molecule to the patient
University of Sheffield, June 2005, Sheffield, UK

Stolzing, A.
Grant: EPSRC Pilot Summer Programme
July–October 2006

zur Nieden, N.I.
Travel cost grant: McLaughlin Foundation
2005

zur Nieden, N.I.
Postdoc of the Year 2005, Leica Meritorious Performance Award
2005, University of Calgary, Canada

zur Nieden, N.I.
Travel cost grant: Canadian Institutes of Health Research (CIHR) Training Program in Genetics, Child Development and Health
2006

zur Nieden, N.I.
Travel cost grant: Graduate Studies Education
2006, University of Calgary, Canada

zur Nieden, N.I.
Travel cost grant: Canadian Stem Cell Network Centres of Excellence
2006

zur Nieden, N.I.
Alumni Award: Canadian Stem Cell Network Centres of Excellence
2006

Patents

Boltze, J; Emmrich, F.; Kowalski, I. & Blunk, J.
Device and method for the detection of specific behavioural anomalies in experimental animals
Ref: 10 2004 029 971.4, IPC Hkl A61B 5/16, Nkl 5/103

Emmrich, F.
Application of a monoclonal antibody to treat an autoimmune disease
Ref: 06F47048–IZI

Sack, U.; Bold, A. & Wurth R.
Method for quantifying a cell population of interest contained in a human blood sample
Ref: 06F47124–IZI-EP

Exhibitions and Conferences

P PO represented with posters
PA represented with papers
IS represented with an information stand

2005

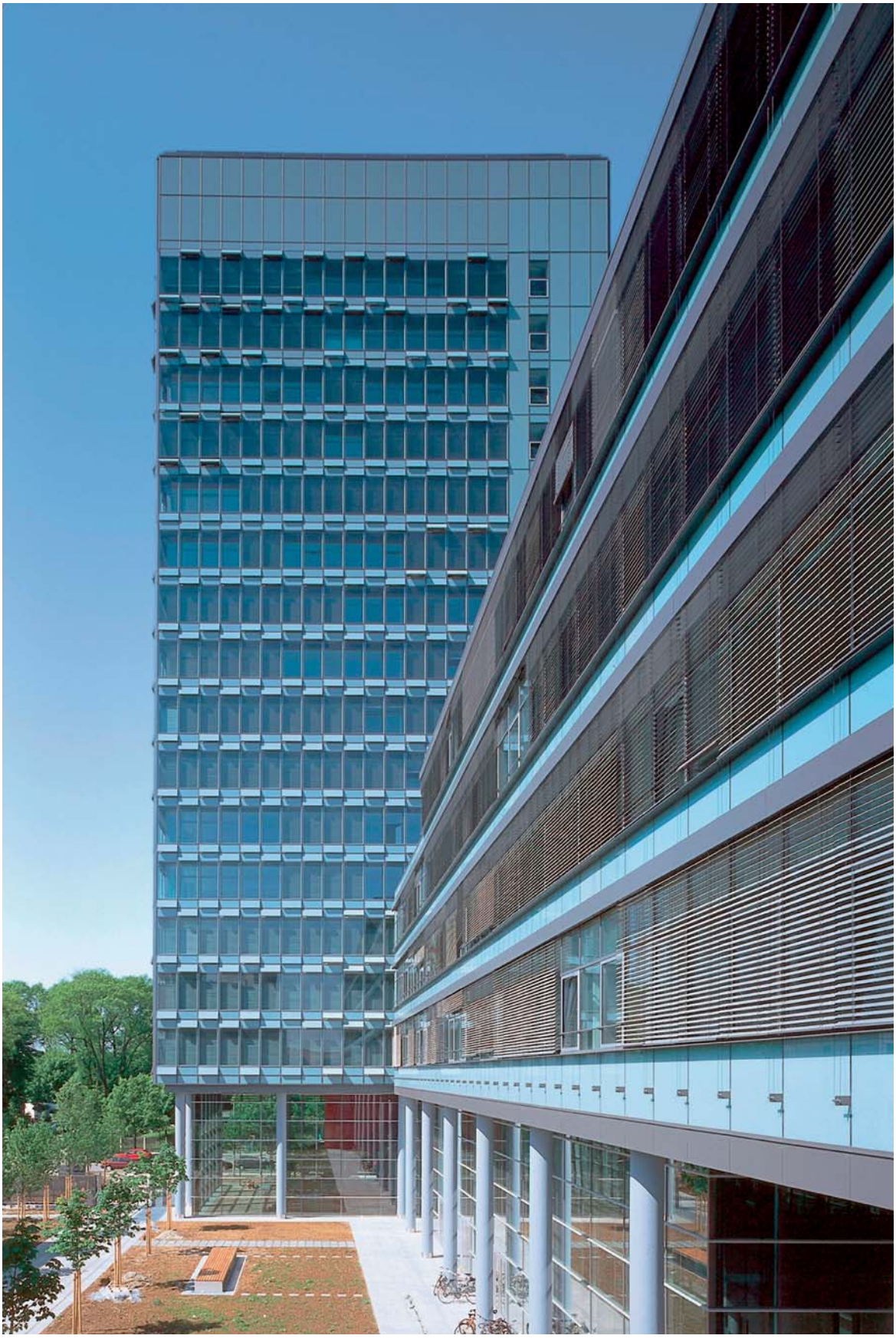
P	Keynote Seminar: Molecular Regulation of Stem Cells, February 2005, Banff, Canada The 10th Leipzig Workshop on System Biology and Clinical, April 2005, Leipzig Cytomics, April 2005, Leipzig 2nd World Congress on Regenerative Medicine, May 2005, Leipzig
PA	British Society for Matrix Biology Autumn Meeting Joint with the UK Tissue & Cell Engineering Society, June 2005, Bristol, UK Annual European Congress of Rheumatology EULAR 2005, June 2005, Vienna, Austria
P	International Society for Stem Cell Research 3rd Annual Meeting, June 2005, San Francisco, CA, USA
PA	43rd Conference of the Laboratory Animals Society, September 2005, Berlin Presymptomatic Tumour Diagnosis Innovation Forum, September 2005, Dresden 4th Immunodiagnostic Meeting, September 2005, Dresden First German Working Meeting of the EASI Initiative, September 2005, Kiel
PA	Tissue, Cell & Engineering Society Conference, September 2005, Leeds, UK
PA	Strategies for Engineered Negligible Senescence (SENS), Second Conference, September 2005, Cambridge, UK
PA	9th Interdisciplinary Child Immunology Working Meeting, October 2005, Höfgen-Kaditzsch
PA	15th Annual Meeting of the German Society for Cytometry, October 2005, Leipzig
IS	Biotechnika 2005, October 2005, Hanover
P	18th World Congress of Neurology, November 2005, Sydney, Australia
PA	Workshop Bead-Arrays, November 2005, Leipzig Canadian StemCellNetwork 4th Annual General Meeting, November 2005, Calgary, Canada

2006

PA	Centre Biomaterials Tissue Engineering workshop on tissue engineering of bone, January 2006, Sheffield, UK
PA	1st Annual Stem Cells and Regenerative Medicine Symposium, January 2006, Burlingame, CA, USA ERA-NET Partnering Workshop, January/February 2006, Hohenkammer 27th German Cancer Congress, March 2006, Berlin
PA	Fifth Immunodiagnostic Meeting, March 2006, Dresden Annual Conference of IGLD (Interdisciplinary Group for Laboratory and Flow Cytometry), March/April 2006, Göttingen
PA	Regenerate: World Congress on Tissue Engineering, April 2006, Pittsburgh, USA Analytika 2006, April 2006, Munich Antibody Therapy in the 21st Century, April 2006, Hanover 72nd annual conference, Mannheim, German Society for Carpological and Cardiovascular Research, April 2006, Mannheim
IS	Bio 2006, April 2006, Chicago, USA
P	International Society for Cell Therapy, May 2006, Berlin
P	8th International Congress of the Cell Transplantation Society, May 2006, Milan, Italy
P	87th German X-ray Congress 2006, May 2006, Berlin
P	5th Biotechnology Symposium 2006, May 2006, Leipzig
IS	International Society for Cell Therapy, May 2006, Berlin
IS	Biotechnology Days, May 2006, Leipzig
PA/P	Strategies in Tissue Engineering, May/June 2006, Würzburg
P	FEBS Special Meeting: Cellular Signalling, May/June 2006, Dubrovnik, Croatia
P	Human Genome Meeting 2006, June 2006, Helsinki, Finland IVVDC International Veterinary Vaccines and Diagnostics Conference 2006, June 2006, Oslo, Norway The first Franco–German Meeting 'RNA Technologies: New Prospects for Future', June 2006, Berlin Th1/Th2-Meeting, June 2006, Marburg
PA	1st UK Mesenchymal Stem Cell Meeting, June 2006, York, UK

P/PA	3rd Annual Canadian Biomaterials Society Meeting, May 2006, Calgary, Canada International Society for Stem Cell Research 4th Annual Meeting, June 2006, Toronto, Canada
IS	Stem Cells Congress, June 2006, London, UK
P	RNA 2006 Annual Meeting, July 2006, Seattle, USA The 19th International Pig Veterinary Society Congress, July 2006, Copenhagen, Denmark
P	International Leopoldina and DFG (German Research Foundation) Conference on Stem Cell Research, September 2006, Dresden RNAi & High-Content Screening Applied to Target Discovery, September 2006, Berlin
P/PA	European Immunology Congress, September 2006, Paris, France 5th Benjamin Franklin Stem Cell Workshop, Karl Landsteiner Lecture, September 2006, Berlin International Conference Embryonic and Somatic Stem Cells – Regenerative Systems for Cell and Tissue Repair, September 2006, Dresden
P	EuroStemCell Meeting, September 2006, Lausanne, Switzerland 1st Joint Meeting of European National Societies of Immunology, 16th European Congress of Immunology, September 2006, Paris
P	Fraunhofer Life Science Symposium, October 2006, Leipzig
PA	IZBI (Interdisciplinary Centre for Bioinformatics) Autumn Seminar, October 2006, Chribska, Czech Republic DGHO (German Society for Haematology and Oncology) Congress, October 2006, Leipzig
PA	10th Interdisciplinary Child Immunology Working Meeting, October 2006, Höfgen-Kaditzsch microRNAs Europe 2006, November 2006, Cambridge, UK
P	Translational Control and Non-Coding RNA Meeting, November 2006, Nove Hrady, Czech Republic
PA	1st Congress of the German Society for Stem Cell Research, November 2006, Cologne
P	Canadian StemCellNetwork 5th Annual General Meeting, November 2006, Ottawa, Canada 5th International Congress on Autoimmunity, November/December 2006, Sorrento, Italy
P	Leipzig Research Festival for Life Sciences, December 2006, Leipzig Veterinary Vaccines, December 2006, Hamburg

Introducing the Fraunhofer Society



Aims and Principles

The Fraunhofer Society 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 aims to promote the development of a society which is economically successful without losing sight of social welfare or environmental responsibility.

The Fraunhofer Society was founded in 1949 and is a recognized non-profit organization. Its members include prestigious companies and private patrons, who help shape the Fraunhofer Society's research policy and strategic development.

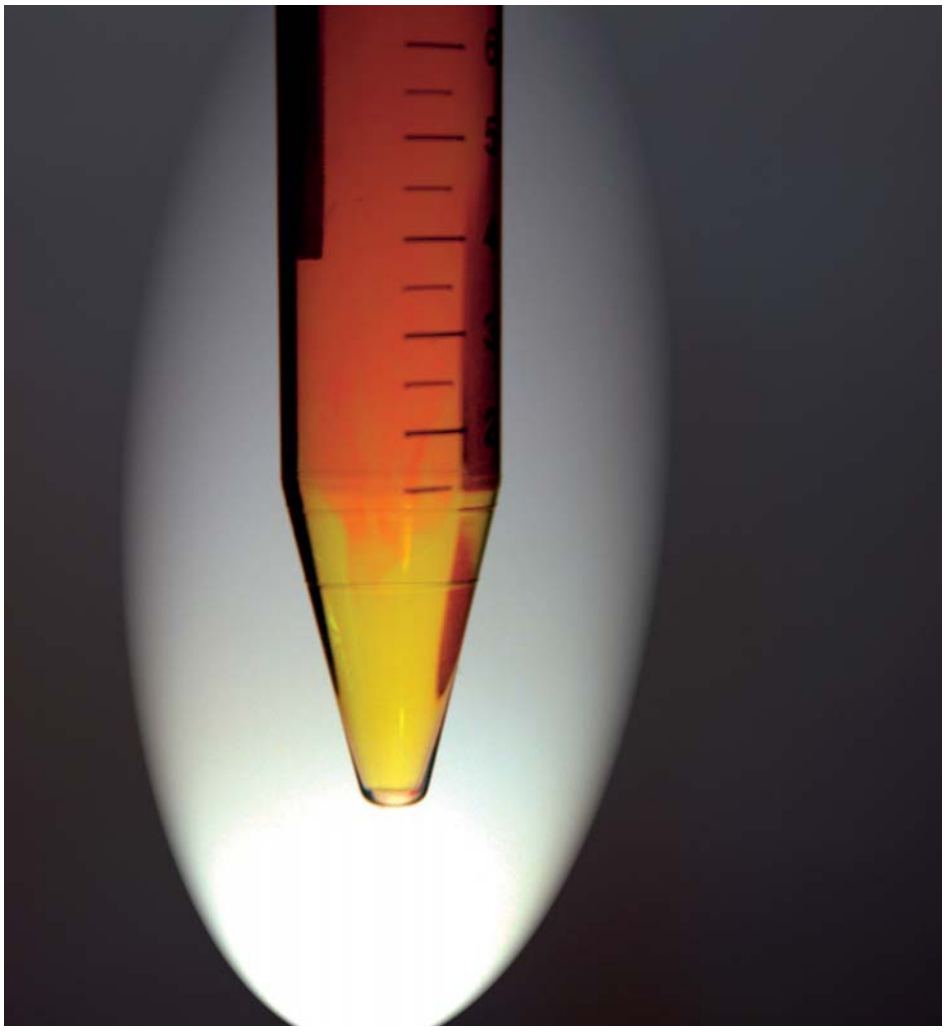
The organization was named after Joseph von Fraunhofer (1787–1826), an optician from Munich, who became a successful researcher, inventor and entrepreneur.

Structure

The Fraunhofer Society maintains 58 institutes with around 80 research units at more than 40 locations in Germany. The vast majority of the nearly 13,000 staff are qualified scientists and engineers. They work with an annual research budget of more than € 1.2 billion, over € 900 million of which is generated through contract research. Roughly two thirds of the Fraunhofer Society's research revenue stems from industry contracts and publicly financed research. The remainder is contributed by national and regional government, partly as a means of enabling the institutes to pursue fundamental research in areas that are only likely to become relevant to industry and society within five or ten years.

Affiliated research centres and branches in Europe, the USA and Asia enable contact to the main regions of current and future scientific progress and economic development.

As an employer, the Fraunhofer Society 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.



The Life Sciences Alliance

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

To strengthen the biosciences, biomedicine and biotechnology, in 2001 the Fraunhofer Life Sciences Alliance was created, originally comprising IBMT, IGB, IME and ITEM – and joined in 2005 by IZI.

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

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

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

Alliances in the Fraunhofer Society

- Information and Communication Technology
- Microelectronics
- Production
- Materials and Components
- Life Sciences
- Surface Technology and Photonics
- Defence and Security

Institutes in the Life Sciences Alliance

Institute for Biomedical Engineering (IBMT)	Ensheimer Strasse 48 D-66386 St. Ingbert Tel: +49 (0)6894 9800 Fax: +49 (0)6894 980400 Email: info@ibmt.fraunhofer.de
Institute for Interfacial Engineering and Biotechnology (IGB)	Nobelstrasse 12 70569 Stuttgart Tel: +49 (0)711 970 4001 Fax: +49 (0)711 970 4200 Email: info@igb.fraunhofer.de
Institute for Molecular Biology and Applied Ecology (IME)	Forckenbeckstrasse 6 52074 Aachen Tel: +49 (0)241 60850 Fax: +49 (0)241 6085 10000 Email:info@ime.fraunhofer.de
Institute of Toxicology and Experimental Medicine (ITEM)	Nikolai-Fuchs-Strasse 1 Main entrance: Stadtfelddamm 30625 Hannover Tel: +49 (0)511 53500 Fax: +49 (0)511 535 0155 Email: sekretariat@item.fraunhofer.de
Institute for Cell Therapy and Immunology (IZI)	Deutscher Platz 5e 04103 Leipzig Tel: +49 (0)341 355360 Fax: +49 (0)341 3553 6109 Email: info@izi.fraunhofer.de

Core Competencies of the Life Sciences Alliance

- Accelerated drug development
- Regenerative medicine
- Production and safety of foods and animal feed
- Biotechnical production, evaluation and testing of substances

Head of the Alliance Office:

Dr Claus-Dieter Kroggel
Institute of Toxicology and Experimental Medicine

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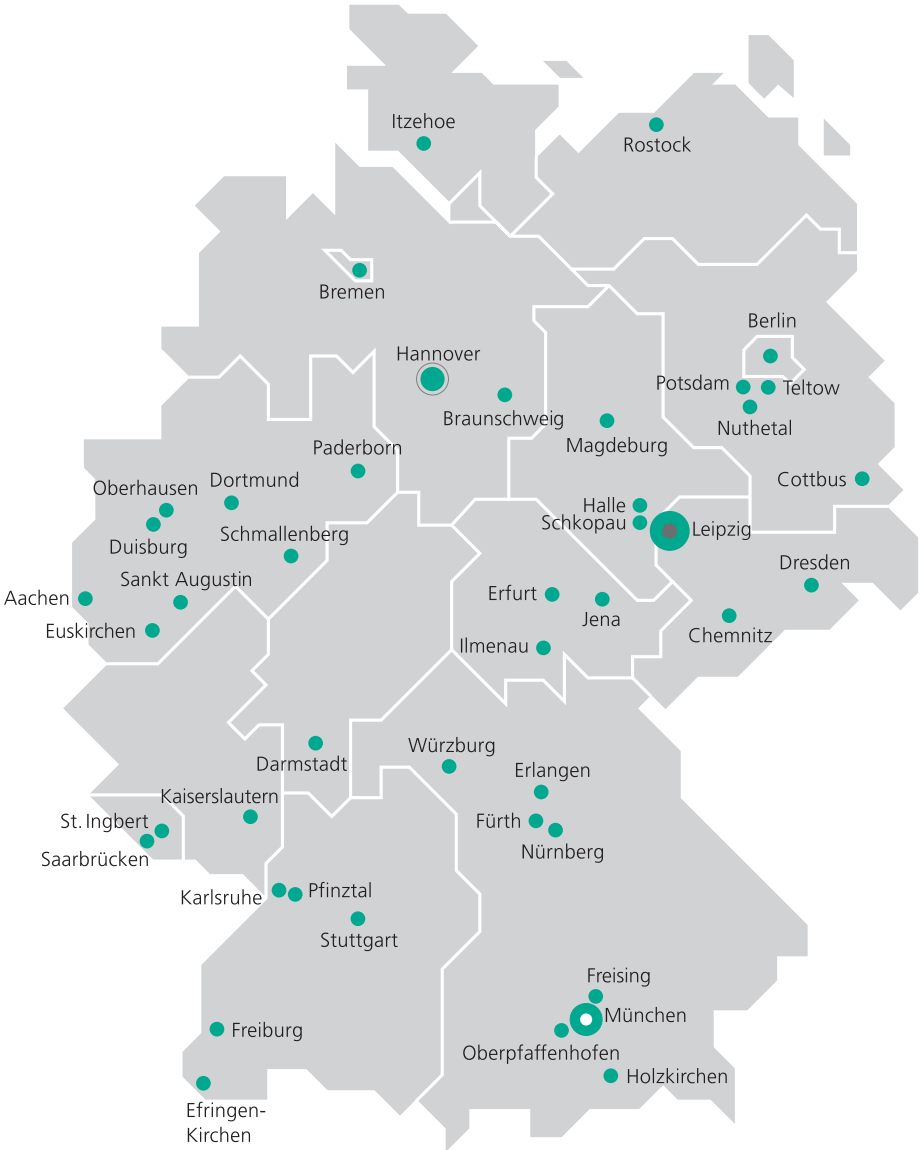

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Central office of the
Life Sciences Alliance, Hanover

IZI, Leipzig

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We would be delighted to send you more details about IZI, our current projects and possibilities for future cooperation. Simply fill in and tear out the postcards below, and send them to us.

Alternatively, send a fax to
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Öffentlichkeitsarbeit
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04103 Leipzig
Germany

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- ☐ Information on the Life Sciences Alliance
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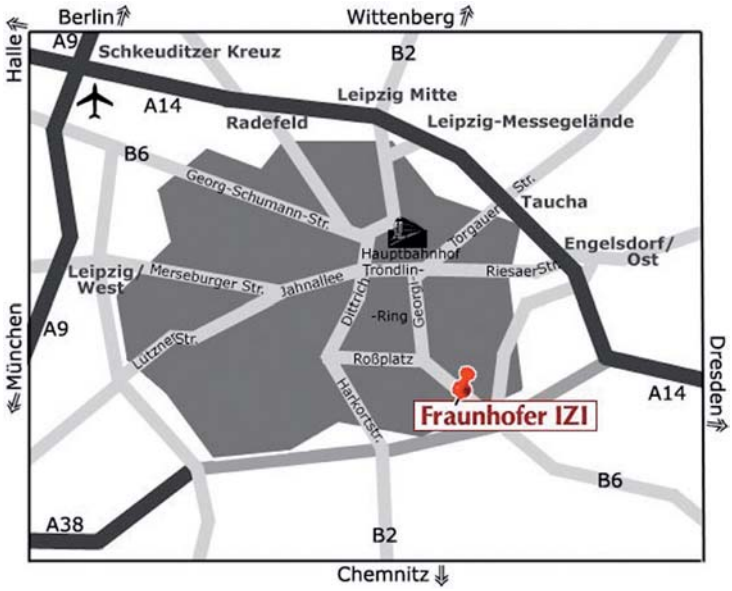
Travel Directions



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Reaching IZI by car

A 9 — Exit the motorway at Leipzig-West
Take the B181 heading for "Zentrum", follow the B87
(Merseburger Strasse, Lützner Strasse, Jahnallee),
after central railway station turn right towards Augustusplatz (Leipzig Opera House),
then take Prager Strasse, turn off towards Alte Messe

A 14 — Exit the motorway at "Leipzig-Mitte"
Take the B2 (via Maximilianallee) heading for the city center (Zentrum),
follow the B2 (via Gerichtsweg and Prager Strasse), exit from Prager Strasse towards Alte Messe

A 38 — Exit the motorway at "Leipzig-Süd"
Take the B2 direction heading for Leipzig "Zentrum",
turn off into Richard-Lehmann-Strasse,
follow Richard-Lehmann-Strasse and exit before the BMW car show room towards Alte Messe

Reaching IZI by public transport

By rail — Travel to Leipziger Hauptbahnhof (Leipzig Central Station), take the no. 16 tram heading for Lössnig, alight at Deutsche Bücherei (main entrance to BioCity) or An den Tierkliniken (rear entrance to BioCity)

From the airport

Take the train to Leipzig Hauptbahnhof (Leipzig Central Station) then continue by tram (see above)

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