touch
At a glance: 3 research programs within the program-oriented funding (POF) framework of the Helmholtz Association of German Research Centres 760 publications (2008) 51 doctoral degrees in conjunction with various universities (2008) 122 patent families 79 license agreements 1680 staff members 40 trainee positions 28 research institutes and departments 198 million euros (2008) finance volume 52-hectare research campus to the north of Munich

Helmholtz Zentrum München is a member of Germany’s largest scientific organization, the Helmholtz Association of German Research Centres. With 28,000 employees and an annual budget of 2.8 billion euros, its mission is to pursue long-term research objectives on behalf of government and society. The insights and knowledge gained by the Helmholtz Association help to preserve and improve the foundations of human life.
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Helmholtz Zentrum München
Research at the interface of health and the environment
Helmholtz Zentrum München is the German Research Center for Environmental Health. As leading center oriented toward environmental health, it investigates complex diseases which develop from the interaction of environmental factors, lifestyle and individual genetic disposition. Metabolic and respiratory diseases, neurodegeneration, diseases of the immune system and other chronic diseases are our main areas of research interest. Through a better understanding of disease mechanisms, we aim to develop innovative approaches for prevention, diagnosis and therapy.
We are dedicated to advancing research. Young people are our scientific potential.

Postdocs and PhD students from all over the world make up half of our scientific staff. Their competence and motivation are the cornerstones of our international competitiveness. We support and mentor our junior researchers and thus invest in the future.

Alexander Mannes (Institute of Clinical Molecular Biology and Tumor Genetics) 
Ramona Böhm (Comparative Medicine Department) 
Andrea Braun (Clinical Cooperation Group «Environmental Dermatology and Allergology») 
Teresa Neumaier (Institute of Radiation Protection) 
Michael Telgkamp (Institute of Bioinformatics and Systems Biology)

The photo was taken on the Panzerwiese across from the research campus.
2008 was a successful and dynamic year for the strategic reorientation of the center. As of January 1st we changed our name to Helmholtz Zentrum München – German Research Center for Environmental Health. The renaming reflects our aim to become the world’s leading center in the field of environmental health research.

The new name also documents that we are a member of the Helmholtz Association of German Research Centres and underscores our commitment to Munich as research location. At a festive event in the presence of Bavaria’s Minister President Dr. Günther Beckstein, Helmholtz Association President Prof. Dr. Jürgen Mlynek and representatives of the Federal Ministry of Education and Research (BMBF), we presented our goals and our strategy to a wide circle of partners.

A further milestone was securing our financing. In 2007 and 2008 we focused our efforts on this important issue and are now in an excellent starting position to carry out our endeavors. The evaluation for the second period of program-oriented funding (POF) of the Helmholtz Association completely confirmed our successful reorientation. The Helmholtz Senate concurred with this positive assessment made by the international panel of experts. For the period from 2009 to 2013 our center will receive a total of 496 million euros as allocation for its basic operational financing. The evaluators and the Senate have thus clearly approved the strategy of the center with its focus on health research. With environmental health we associate the interaction of environmental factors, living conditions and genetic information in the context of human health as well as the development and treatment of chronic diseases such as lung diseases, diabetes or neurodegenerative diseases. With this new focus our research center enjoys a unique position in the international research landscape.

The investigation of lung diseases will be a main focus of our research work in the future. In this context, building up the Comprehensive Pneumology Center together with the Ludwig-Maximilians-Universität Munich (LMU) and the Asklepios Specialist Hospital in Gauting is a key aspect of this endeavor. On November 1st we were able to establish the Institute of Lung Biology and Disease headed by Prof. Dr. Oliver Eickelberg, which together with the new Institute of Cli-
nical Pneumology (the director is still to be appointed) will form the core of the new translational center for lung research. Hence, we are making a major contribution to closing the research gap of this medically and economically increasingly important disease complex. In doing so, we are ensuring that new treatment approaches will be quickly available to patients.

Other main research areas will be metabolic diseases, in particular diabetes mellitus, diseases of the immune system and mechanisms in neurodegeneration, cancer and chronic diseases. We have made marked achievements in these fields as well.

— In building up our research focus on diabetes we have made major steps forward in our chosen course of action. A diabetes task force is preparing the founding of two new clinical cooperation groups together with the university hospitals of Technische Universität München and Ludwig-Maximilians-Universität. A junior research group studying the mechanisms of insulin resistance at the Institute of Experimental Genetics already began work in February. Through resolutions of our Supervisory Board concerning the founding of two new institutes on diabetes research we are in the position to achieve the required critical mass in this field, which is becoming increasingly important for public health. Our activities are paying off: In September Prof. Dr. Annette Schavan, Federal Minister of Education and Research, and the Bavarian Minister President announced the founding of a national diabetes center located in Munich, with Helmholtz Zentrum München as coordinator.

— In the competition for the new foundation of the German Center for Neurodegenerative Diseases in Bonn we were able to achieve a partial success due to our research focus in the field of neurodegeneration: We will participate in building up a partner location in Munich in cooperation with our university partner groups.
In December we signed the founding charter for a joint allergy research center together with Technische Universität München (TUM). This center will house the only chair in Germany for molecular allergology and environmental research.

In conjunction with the establishment of Helmholtz Zentrum München and its strategic orientation on environmental health, the Asse Mine was transferred to the area of responsibility of the Federal Office of Radiation Protection as of January 1, 2009. Since 1964, on behalf of the Federal Government, the former salt mine had been operated by the former Gesellschaft für Strahlenforschung as research mine for the development and testing of end-storage procedures for radioactive waste. Since the middle of the nineties, preparations had been made for closing and filling the mine.

The key performance indicator for a research institution is its output of scientific results. Through impressive publications in prestigious journals we demonstrated the excellence of our center again in 2008. Both the number of publications in peer-reviewed journals and the citations in the scientific community in the form of impact factors have significantly increased during the past year.

Successful publications in renowned journals are also the connecting points for building up national and international cooperation initiatives as well as strategic partnerships. In 2008, a whole array of new large-scale projects could be initiated at our center:

— The »Helmholtz Alliance for Mental Health in an Aging Society« (HelMA), led by Helmholtz Zentrum München, brings together Germany’s leading Alzheimer and Parkinson experts in a collaboration to investigate the causes of neurodegenerative diseases and to develop diagnostic methods and therapeutical approaches.

— Within the framework of the KORA-Age project together with three other university and clinical partners, the long-term influence factors and consequences of multimorbidity in elderly and old people shall be investigated.

— »From Disease Genes to Protein Pathways« is a new consortium project that compares protein interactions in humans and in mice. The findings shall contribute to the elucidation of disease-related signaling pathways and their application in the prevention and therapy of diseases.

— New projects funded by the Federal Ministry of Education and Research include the creation of a mouse model to research alcoholism and two subprojects for the disease-related Competence Network Adiposity, which is striving to improve the scientific basis for the effective prevention of early obesity in children.

— As part of the Roadmap for European Infrastructure funded by the European Commission, Helmholtz Zentrum München participates in three infrastructures in the fields of biosciences and medical research. Here the purpose is to build up infrastructures for phenotyping and archiving genome models in mammals, to establish biosample databases and to provide biomolecular resources as well as biological information.

— Last not least, Helmholtz Zentrum München, together with the German Cancer Research Center (DKFZ), is initiator and coordinator of the Germany-wide »Helmholtz Cohort« in the service of health research. Two hundred thousand healthy citizens shall be included in a new, large-scale population study over a period of ten to 20 years to investigate common chronic diseases such as diabetes, cancer, cardiovascular diseases or dementia diseases. Helmholtz Zentrum München and
the German Cancer Research Center will coordinate the study and plan and carry it out together with universities and other national research institutions.

To ensure the future of our center and to make an active contribution to the improvement of human health and quality of life through excellent research, we rely on the high qualifications and motivation of our staff members. The expansion of our offerings to promote young researchers is of key importance to us:

— Helmholtz Zentrum München’s own doctoral program offers around 300 PhD students an excellent scientific environment in a wide cooperation network with universities, hospitals and other Helmholtz centers. With the establishment of an own office for PhD students and a center-wide Doctoral Students’ Day we have intensified our activities for doctoral students.

— Within the framework of the junior researchers’ program in which we give young researchers the opportunity to head their own research groups, two new groups could be added. Internally, by strengthening the area of human resources development, we want to purposefully support our young employees in their career planning.

— We view the anchoring of equal rights and equal opportunities for men and women to be an essential part of our corporate culture. Last year – for the second time – our center was awarded the Total E-Quality Certificate, which is granted to companies, organizations and universities who offer equal opportunity for men and women.

— Furthermore, in 2008 the new alumni portal linking former staff members to the center was launched. The platform shall serve to build up a national and international network.

In 2008 we placed special emphasis on management processes. We consider the further development of two topics to be the key to the future of our center: our mission statement and corporate governance. Both are essential to successfully implement our center’s strategy and attain our intended objective of becoming the world’s leading center for environmental health by 2013.

The basis of our success is the excellent work and commitment of our staff, and we would like to take this opportunity to express our special gratitude to all of them. We would also like to thank the Supervisory Board and the Scientific Advisory Board for their competent accompaniment of our activities, the Federal Ministry of Education and Research and the Bavarian State Government for their confidence in us and for the allocation of funds. Many thanks also to the President of the Helmholtz Association and the office in Berlin for their active support in communicating our themes and anchoring them in the Helmholtz Association.

Prof. Dr. Günther Wess
CEO and President

Dr. Nikolaus Blum
CFO
1. Our new name reflects our program: Helmholtz Zentrum München — German Research Center for Environmental Health. The new name denotes the position of the center in the research landscape.

8. Tracking down the herpes virus: With the support of the Service Platform for Monoclonal Antibodies, for the first time all proteins of the human herpes virus in infected mammalian cells are identified. The virus is considered to be a trigger of lymphoma and Kaposi’s sarcoma.

15. Reservoir for HIV viruses elucidated: AIDS patients often suffer from neurological diseases. Scientists of the Institute of Virology were able to show that the HIV viruses not only proliferate in the astrocytes of the brain but also in neural precursor cells.

JANUARY

1. Junior research group investigates insulin resistance: In the Institute of Experimental Genetics the new junior research group »Insulin Resistance in Type 2 Diabetes« begins work.

28. The campus celebrates: Together with Bavaria’s Minister President Dr. Günther Beckstein and Helmholtz President Professor Jürgen Mlynek, more than 700 guests celebrate the renaming and the new orientation of our center.

Fig. 1

MARCH
1. Adiposity and alcoholism are studied: The Federal Ministry of Education and Research funds etiological research at the molecular level on adiposity, alcoholism and disease-related signaling pathways.

28. Total E-Quality in the center: Helmholtz Zentrum München is distinguished for its human resources policy oriented towards equal opportunity for women and men. Fig. 3

5. Studying in Bavaria: Helmholtz Zentrum München joins Studieren-in-Bayern, an alliance of associations and research institutions. Fig. 2

7+8. Program-oriented funding (POF) evaluated: International experts evaluate the applications of Helmholtz Zentrum München for the second phase of program-oriented funding of the Helmholtz Association of German Research Centres.

12. Cornelia Pieper visits the center: The deputy chairman of the Research Committee of the German Parliament discusses research funding and results transfer. Fig. 4
7. HelMA is launched: Leading Alzheimer and Parkinson experts study neurodegenerative diseases in the Helmholtz Alliance for Mental Health in an Aging Society (HelMA).

15. SAP test phase begins: The new SAP Business Suite software is tested prior to its launch in 2009.

16. Perspective for Chemical Biology: A scientific symposium on Chemical Biology is held at the center.

21.–23. Mathematics for the biosciences: The Institute of Biomathematics and Biometry celebrates its tenth anniversary.

30. From gene to protein: The Proteomics Core Facility in the Genome Analysis Center and the new founded Protein Analytics Department are launched. Fig. 5

1. Department of Zebrafish: The Department of Zebrafish Neurogenetics becomes an independent research department. Fig. 7

1. Diabetes research boosted: The Federal Ministry of Education and Research funds the identification of new metabolite markers within the Competence Network on Diabetes.

19. Research site inspected: Climate change and sustainable soil utilization: Bavaria’s Minister President Dr. Günther Beckstein visits Scheyern Experimental Farm. Fig. 6

30. From gene to protein: The Proteomics Core Facility in the Genome Analysis Center and the new founded Protein Analytics Department are launched. Fig. 5
1. Translational Center for Lung Research is established: Oliver Eickelberg heads the new pulmonary research institute as part of the Comprehensive Pneumology Center (CPC). Fig. 8

5. Germany’s Federal Cabinet decides on Asse transfer: In 2009 the Federal Office of Radiation Protection will be responsible for the Asse Mine.

13. Innovative prevention research: The first Helmholtz Forum on Health presents new approaches in preventive research.

15. Alumni form a network: Via the platform www.helmholtz-muenchen.de/alumni former staff members and active staff members can keep in touch and intensify their contacts.

17. Exchange of ideas on Science Day: Staff members report on excellent research results and communicate new concepts that transcend institute borders. Fig. 9

18. Information exchange for PhD students: Doctoral Students’ Day provides suggestions for PhD students and their supervisors. Abb. 10

18. Awards for dissertations: Three doctoral students receive the prize of the Association of Friends and Supporters (VdFF) of Helmholtz Zentrum München. Fig. 11

19. Concepts for joint research: The cooperation partners of the planned Comprehensive Pneumology Center (CPC) present their research proposals.

1. Studies on diseases in old age: KORA-Age studies myocardial infarction, stroke and diabetes in Augsburg residents over 65 years.


2. Munich chosen as location for diabetes research: Germany’s Education and Research minister Prof. Dr. Annette Schavan announces the founding of a national diabetes center at Helmholtz Zentrum München.


24. Helmholtz Senate approves Helmholtz cohorts. Diabetes, cancer, cardiovascular diseases or dementia diseases: 200,000 citizens will be screened for chronic diseases.

5. Board and council approve strategy: The Supervisory Board and the Scientific Council give green light for founding two institutes to research type 2 diabetes.

10. Star tenor for leukemia research: José Carreras visits the clinical cooperation group »Hematopoietic Stem Cell Transplantation« at the University Hospital Munich-Grosshadern.

12.+13. Genome research meets medicine: The research networks NGFN-Plus and NGFN-Transfer position themselves within the grant program of medical genome research.

17. Munich strengthens allergy research: Technische Universität München and Helmholtz Zentrum München agree on a joint research center on allergy and the environment.
We explore the relationships between environmental factors, lifestyle and genetics.
Metabolic diseases such as the increasingly prevalent type 2 diabetes are a consequence of the complex interaction between genetic disposition and unfavorable living conditions. Scientists of Helmholtz Zentrum München and Ludwig-Maximilians-Universität Munich have for the first time shown an association between the genetic makeup of an individual and his/her metabolism. With the aid of metabolomics the research team was able to capture a detailed ‘snapshot’ of the physiological constitution of the body.

For the study the research team combined the genetic data of 284 test subjects with the lab results containing several hundred metabolite values of these test subjects. By comparing the genetic and metabolite data, mutations could be identified for the first time on a genome-wide level, resulting in four genes which are respectively associated with a characteristic trait of the metabolic processes. It is not by chance that these four genes are concerned, as they play a key role for the body’s metabolism. They encode enzymes that are important in particular for the lipid metabolism.

In the group of test subjects, individuals had different gene variants and were found respectively also to present different characteristic traits in certain metabolic processes, including the synthesis of polyunsaturated fatty acids which play an important role for the cardiovascular system. From this the scientists could derive genetically determined metabolite patterns. Analogous to the term genotype, which encompasses the genetic features, the metabolite patterns which were identified in the test subjects could be called metabotypes (genetically determined traits of metabolism).
Tailoring Drugs to Individuals

Research results indicate that metabolomics is the key for tracking the effects of gene mutations. This especially applies when genes are altered that encode enzymes and thus play an important role in human metabolism.

In the future, metabotypes may help to identify health risks for certain diseases in a much more differentiated way than has been possible until now based on gene analyses – especially for diseases that are closely associated with metabolism. These include common diseases such as diabetes, gout or a narrowing of the coronary vessels which often leads to stroke or myocardial infarction. With knowledge of such metabotypes, patients can be treated in a more targeted manner in the future, because their reactions to drugs and also the influence of nutritional and environmental factors can be more precisely assessed against this background. These findings could result in a step towards personalized health care and nutrition.

HIGHLIGHTS

Prof. Dr. Karsten Suhre
Since 2006: Research Group Leader »Metabolomics«, Institute of Bioinformatics and Systems Biology, Helmholtz Zentrum München, Professor of Bioinformatics at Ludwig-Maximilians-Universität Munich (LMU)
1994–2006: Researcher at Centre National de la Recherche Scientifique (CNRS) in Toulouse and Marseille and in the automobile industry (Karmann 2000–2001)

Original Publication:
Scientists of Helmholtz Zentrum München have identified variants in the genome which occur in individuals with low uric acid concentrations more frequently than in the normal population. The uric acid level is an important marker for gout. Likewise, it is also frequently associated with other metabolic diseases.

A team of scientists from the Institute of Epidemiology and the Institute of Human Genetics of Helmholtz Zentrum München and from the University of Innsbruck and the University of Greifswald have identified a gene involved in the regulation of the uric acid concentration. The research group led by Angela Döring, Dr. Christian Gieger and Dr. Christa Meisinger investigated the association between gene variants and uric acid levels in the normal population. Here DNA chips were used which enable the determination of 500,000 of the most frequent variants of the human genome. This genome-wide comparison of frequent variants with uric acid levels — also called a genome-wide association study — was conducted with 1644 individuals from the KORA study (Cooperative Health Research in the Region of Augsburg). The role of the genetic variants could be confirmed in three further independent studies.

Since gout runs in families, scientists early on assumed that there was a genetic component in the development of the disease. The studies of the research group show that variants in the SLC2A9 gene are associated with low uric acid levels. The association is stronger in women than in men. Expression studies were able to show that one isoform of the gene explains 15% of the variance of the uric acid concentration in women; in men the effect is less.

An elevated uric acid level is the cause of gout and is furthermore associated with cardiovascular diseases, diabetes, overweight or the metabolic syndrome. The excess of uric acid in the se-
Sodium can be deposited in the form of small crystals in the joints and soft tissue. This can lead to gout with severe pain attacks and can be observed already at levels between 6–7 mg/dl. In the Augsburg population, 15% of the 25- to 64-year old men have an uric acid concentration of over 7 mg/dl, while only 1% of women in this age group have uric acid levels that are that high. Generally, pre-menopause women are far less often affected by gout attacks than men. However, after menopause, the incidence increases in women as well.

Besides variants in SLC2A9, different causes for an elevated uric acid concentration are known. These include such lifestyle factors as alcohol consumption or high meat consumption as well as diseases or intake of medications which are associated with elevated cell degradation and/or a decreased uric acid excretion in the kidney. In addition, an elevated intake of fructose causes a clear increase in uric acid. What exact role the gene plays in the complex regulation of excretion in the kidney and/or in the production of uric acid in the cell for nucleic acid degradation must now be intensively elucidated in order to understand the cell biological relationships in the development of hyperuricemia.
How Stress Makes Cells Age

Scientists at Helmholtz Zentrum München have deciphered the molecular mechanisms that trigger cell death in response to oxidative stress. These insights unveiled new targets for intervention in the aging process and in the treatment of degenerative diseases.

The fact that oxidative stress is a major inducer of cell death is a well-accepted current model. Until now, however, the source and nature of reactive oxygen species (ROS) and questions concerning the way they act in cell death signaling have remained obscure. To find answers to these questions, the research group led by Marcus Conrad at the Institute of Clinical Molecular Biology and Tumor Genetics set out to elucidate the molecular function of the prevailing cellular reducing agent, glutathione, in the metabolic pathway of cell death.

Therefore, the researchers generated mice and cells that specifically lacked glutathione peroxidase 4 (GPx4) – GPx4 is emerging as one of the most important glutathione-dependent enzymes in mammals. The inducible inactivation of GPx4 caused massive oxidation of lipids and cell death. Pharmacological and genetic analyses revealed that lipid peroxides in GPx4-depleted cells do not appear by accident but accumulate due to the uncontrolled activation of a specific enzyme of the polyunsaturated fatty acid metabolism, 12/15-lipoxygenase. Activation of apoptosis-inducing-factor (AIF), evidenced by its relocation from mitochondria to the cell nucleus, was identified as another important downstream event in this signaling cascade.

So far, it was believed that oxidative stress causes a nonspecific oxidation of many essential cellular biomolecules such as proteins and lipids. Contrary to general expectations, however, the researchers found that apparently through the lack of glutathione or GPx4, a distinctive signaling pathway is engaged which sparks cell death.

If the equilibrium in the organism moves towards oxidative processes, this is known as oxidative stress. Among other things, oxidative stress has been associated with the aging of body cells.
Slowing Aging Processes

The data represent the first molecular analysis of a redox-regulated signaling pathway, describing how oxidative stress is specifically recognized in the body and eventually triggers cell death.

Since this cell death cascade can be interrupted by drugs at each individual step, these findings provide novel cues for the targeted treatment of many oxidative stress-related human diseases.

Acute and chronic degenerative diseases such as stroke, arteriosclerosis, diabetes, Alzheimer’s and Parkinson’s diseases have been linked to high levels of oxygen radicals. Hence, low cellular concentrations of glutathione due to acute or chronic cellular stress may induce the activation of this cell death signaling pathway.

Dr. Marcus Conrad
Since 2005 Research Group Leader, Institute of Clinical Molecular Biology and Tumor Genetics
Until 2005 Project Leader, Department of Comparative Medicine
Until 2004 Junior Researcher, Helmholtz Zentrum München
2001 PhD, Ludwig-Maximilians-Universität München

Original Publication:
Respiratory System [Highlights]

We investigate gene-environment interactions and their importance for breathing.

From L to R
Teresa Neumaier (Institute of Radiation Protection) / Christine Moll (Comparative Medicine Department) / Andrea Braun (Clinical Cooperation Group »Environmental Dermatology and Allergology«)

The photo was taken in the free space between the cafeteria and the computer center.
Scientists of Helmholtz Zentrum München and the Department of Dermatology and Allergology of Technische Universität München have discovered a gene that is important for the development of allergies. The FCER1A gene was discovered at Helmholtz Zentrum München by using state-of-the-art technology with which the entire human genome can be searched.

Immunoglobulins (antibodies) are proteins that mark exogenous agents as invasive pathogens and thus make them visible for the immune system. Defense cells recognize the marked invaders and render them harmless. Different classes (isotypes) of immunoglobulins are present in different compartments of the body and have different tasks. Antibodies of the class IgE mediate protection against parasites, for example worms, but they can also direct themselves against per se harmless environmental allergens and thus lead to allergies.

Why some people are insensitive to allergens during their whole life and others suffer from allergies has not yet been fully elucidated. It is known, however, that genetic factors play a crucial role in the development of allergies. Persons with allergies generally have a higher proportion of antibodies of the class IgE than healthy individuals. These IgE antibodies are usually important for the defense against parasites, but in allergic individuals they are directed against environmental substances such as house dust mites and pollen, which for most people are harmless. The antibodies are bound via specific IgE receptors to specific cells, preferably in the skin or mucous membranes. Through the coupling to membrane-bound IgE receptors, the IgE production is intensified. Upon contact with the allergen, substances are released from the cells, leading to the known allergic symptoms such as allergic rhinitis (hay fever), atopic dermatitis (neurodermitis) or asthma.

The newly discovered FCER1A gene contains the blueprint for the alpha chain of the high-affinity IgE receptor, which plays a key role in the development of allergy. The alpha chain of this receptor is the binding site for immunoglobulin E (IgE) antibodies. The research team led by Dr. Stephan Weidinger, Technische Universität München, and Dr. Thomas Illig, Institute of Epidemiology, discovered that certain variants of the identified gene decisively influence the production of IgE and thus the course of the allergy. The study is based on investigations on the genome of more than 10,000 adults and children throughout Germany.
Most of the test subjects of the study originate from the population studies of the KORA research platform (Cooperative Health Research in the Region of Augsburg), headed by Prof. Dr. Dr. H.-Erich Wichmann, director of the Institutes of Epidemiology at Helmholtz Zentrum München and at Ludwig-Maximilians-Universität Munich. The allergological and dermatological examinations were performed in cooperation with the Department of Dermatology and Allergy of Technische Universität München under the supervision of Prof. Dr. Dr. Johannes Ring.

The new findings on the regulation of IgE antibody production allow deeper insights into the mechanisms of the development of allergies and open up new therapy options. Since autoimmune diseases are likewise associated with IgE antibodies, these findings will not only benefit persons with allergy.

The IgE receptor on antigen-presenting cells consists of one alpha, one beta and two gamma chains. The alpha chain binds IgE, while beta and gamma subunits are important for signal transduction. Certain variants of the gene that encode for the alpha chain (FCER1A) influence the IgE level in blood serum, which itself is associated with allergic diseases.
Allergic diseases are more common in children who live near busy roads. This is the result of a study led by Helmholtz Zentrum München of several thousand Munich children. The authors evaluate the results of their study as clear evidence of the adverse effects of traffic-related air pollutants on the development of allergies and other atopic diseases.

In a longitudinal study lasting six years, the German research group investigated whether there was a correlation between the level of traffic-related air pollutants and the incidence of atopic diseases. The scientists based their analysis on the respective distance of the parental home to roads busy with traffic as well as on computer-modeled values of the concentrations of fine dust, diesel soot and nitrogen dioxide with respect to the residential address of the children.

The research team led by Dr. Joachim Heinrich and Prof. Dr. H.-Erich Wichmann, Institute of Epidemiology of Helmholtz Zentrum München and Institute of Epidemiology of Ludwig-Maximilians-Universität Munich compared the data of approximately 3000 six-year-old children from Munich and surroundings. In two German birth cohort studies (GINI and LISA) the development of these children is being tracked from birth to age six. The studies are coordinated by Helmholtz Zentrum München with the goal of identifying behavioral and environmental risk factors for allergic diseases. The results of medical examinations and regular parental questionnaires were included in the current analysis. Furthermore, at age six the children were tested for the presence of specific IgE antibodies against common allergens in blood serum.

Using computer models, Verena Morgenstern, doctoral candidate at Helmholtz Zentrum München, determined the concentrations of fine dust, diesel soot and nitrogen dioxide for the residential addresses of the children. The results showed that with increasing fine dust exposure, the in-
Incidence of asthma and allergic sensitization to pollen and other common allergens in the outdoor air increased.

Moreover, elevated nitrogen dioxide exposure was linked to an increase in the incidence of eczema. There were clear associations between the residential environment and the incidence of asthma, hay fever, eczema and allergic sensitization: Children who lived less than 50 meters from a road busy with traffic had an up to 50% higher risk for these diseases than children who lived in areas with less traffic. The statistical analysis of the data showed an increasing risk, the closer the children lived to roads busy with traffic.

**Dr. Joachim Heinrich**

*Since 1997 Deputy Director of the Institute of Epidemiology*
*Since 1992 Research Group Leader »Environmental Epidemiology«*
*1990–1992 Epidemiologist at the University of Wuppertal*
*1974–1989 Scientific Assistant and Research Group Leader »Biostatistics« at Erfurt Medical School, Graduate Studies and PhD*

**Original Publication:**

Immune System [Highlights]

We elucidate reactions to endogenous and environmental factors.
Protection Against Infections: What a Single Cell Can Do

Researchers of the Clinical Cooperation Group »Antigen-Specific Immunotherapy« have shown that different cell types can evolve from a specialized T cell. Until now only stem cells were known to have this broad range of development potential.

The aim of the research group is to isolate defined T cells using biotechnological methods so that they can be utilized in treatment of tumor diseases and infections. From patient studies it is known that vaccination with T cells bearing a pathogen-specific receptor can provide effective protection against infection. However, immune cells cultivated in the lab did not turn out to be very effective after transfer to the recipient.

Busch and his colleagues vaccinated mice with only one single pathogen-specific T cell. This T cell was »specialized« to respond to listeria – bacteria that are the cause of the infectious disease listeriosis. Single T cells were extracted from animals that had survived an infection with the bacteria. The research team tracked the path of the single immune cells throughout the bodies of the recipient mice and could observe that first of all, the progeny of a single listeria-specific T cell formed effector cells in the spleen and lymph nodes. Later, the researchers detected the presence of immune memory cells in the spleen, lymph nodes and the lung. The reason why protection against listeriosis could be transferred to mice by single T cells is that the transferred cell generated a number of different T-cell types. Among them are cells that are responsible for the immediate immune response, as well as long-living memory cells, which »memorize« the specific immune response they have once learned. By contrast, in the transfer of cultivated T cells much larger quantities of cells were needed, and the immunization effect was significantly weaker.

After bone marrow transplantation it can take quite a long time for a new immune system to build up protective T cells. During this time infections that are per se harmless can be life-threatening for transplant patients.

A single immune cell is able to put up a »defense shield« against a specific pathogen: The cell divides and generates different immune cell types – short-lived effector cells (SLEC), long-lived central memory T cells (TCM) and effector memory T cells (TEM) – for the different organs and tissues.
Boosting the Immune System

The targeted cell transfer was made possible through an approach called MHC Streptamer, which was also developed by Dirk H. Busch and his team. With this technology individual T cells can be isolated from blood samples — faster and more cost-effectively than with previous methods. Currently this cell transfer is being tested in three clinical trials. First patients that had been treated with a stem cell transplantation and subsequently suffered from Cytomegalovirus (CMV) infection were immunized with merely a few thousand CMV-specific cells of the stem cell donor. Already after a short time they showed an effective immune reaction.

This kind of immunotherapy using the novel cell isolation method appears to be a very promising treatment approach: After the transfer, donor cells trigger a more effective immune response than immune cells which have been harvested from cell cultures. Moreover, dangerous adverse side effects are avoided, because with this method T cells can be harvested in highest purified form. Undesirable T cells could trigger an immune reaction against the foreign organism. However, this does not occur because only the selected pathogen-specific T cells are transferred to the transplant recipients.
Scientists of the Gene Vectors Department were able to show that Epstein-Barr virus alters the properties of a signaling protein of their host cells. The research group led by Dr. Arnd Kieser has succeeded in elucidating a key mechanism of tumor induction by the Epstein-Barr virus.

Viruses use many tricks to gain control over their host cells and to reprogram them to their own advantage. Dr. Arnd Kieser and his colleagues were able to show that Epstein-Barr virus mediates cell proliferation by exploiting a signaling protein of its host cell that usually mediates apoptosis. Epstein-Barr virus (EBV) is a human-pathogenic virus which belongs to the herpes virus family. Its viral genome consists of double-stranded DNA, and it is one of the few known viruses which cause cancer in humans under certain circumstances. EBV-associated cancers include lymphomas (cancer of the lymph nodes), nasopharyngeal carcinoma and gastric cancer.

A protein encoded by the virus, the latent membrane protein 1 (LMP1), is required for the uncontrolled proliferation of EBV-infected cells and thus the development of cancer. Arnd Kieser and his team are studying the molecular mechanism of action of this EBV protein.

LMP1 is a membrane-bound oncoprotein that binds certain signaling molecules of its host cell and thereby critically contributes to the oncogenic transformation of the cells. One of these signal proteins is the factor TRADD. TRADD stands for TNF-receptor 1-associated death domain protein. The scientists used TRADD knockout cell lines which they had established by removing both alleles of the gene from the genome of human B cells in order to demonstrate that TRADD is an essential factor for LMP1 function: In the absence of TRADD, LMP1 can no longer activate NF-κB, a signal transduction pathway which is crucial for cell transformation. Usually, TRADD also induces programmed cell death which is also called apoptosis. Induction of cell death, however, would be
counterproductive for the virus, because it would be adversely affected by the death of its host cell. In fact, the scientists made the surprising observation that TRADD activated by the viral protein LMP1 no longer induces apoptosis.

But how does Epstein-Barr virus manage to specifically switch off the apoptosis function of TRADD? Kieser and his colleagues discovered that the LMP1 protein possesses a unique TRADD binding domain, which recruits the cellular TRADD protein and alters its molecular properties so that the apoptosis signals can no longer be transmitted. Thus, LMP1 masks the apoptosis activity of TRADD. This viral TRADD-binding domain consists of the 16 carboxyterminal amino acids of the LMP1 protein and can be transferred to cellular receptor proteins where it shows the same effects. Hence, Epstein-Barr virus has found a unique molecular way to extinguish an undesired property of a cellular protein in order to adapt this protein to its own needs. This finding might also be the basis for a new therapeutic approach. The scientists surmise that since the specific structure of the LMP1-TRADD interaction is most likely restricted to EBV-infected cells, it might serve as a target structure to develop specific inhibitors which interrupt the transforming signaling cascade of the LMP1 oncogene.

**Highlights**

Epstein-Barr virus encodes the oncoprotein LMP1, which binds signaling molecules of the host cell. When LMP1 activates the signaling protein TRADD, the anti-apoptotic NF-κB pathway is induced and the apoptosis program of the cell is suppressed: The virus-transformed host cell can proliferate further.

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**Original Publication:**


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The molecule p53 is called the »guardian of the genome« because it can suppress cells that are proliferating uncontrollably and can thus inhibit cancer cell growth. However, the molecule p53 also reacts to certain defects in the protein factories of the cell, the ribosomes. It can then cause various disorders in humans and animals, as scientists at Helmholtz Zentrum München collaborating in an international study with colleagues from Stanford University and the University of Michigan were able to demonstrate.

How do light-skinned mice get dark paws, tails and ears? Mutations in the DNA of the mice are responsible for the abnormal pigmentation. However, as the study in the Munich ENU Mutagenesis Project shows, these mutations that were identified by Dr. Helmut Fuchs affect far more than the color of the skin and hair of the mice. The international research team was able to show that two of the genetic mutations impair components of the ribosomes to such an extent that the cellular protein factories cannot or cannot adequately fulfill their functions.

It is already known that defects in certain ribosomal subunits can have a number of consequences. On the one hand, the formation of ribosomes from several components is more difficult, which then affects the production of proteins adversely. Moreover, the lifespan of the affected cells is shortened. Genetically caused defects in ribosomes can also lead to serious disorders such as Diamond-Blackfan anemia in humans. Patients with this innate bone marrow disease do not produce sufficient red blood cells, are delayed in their growth and can develop cranial deformations, among others.

Last not least, the mice with the black paws substantiate this association to ribosomal defects: Closer analysis showed that the animals also suffered from anemia with similar effects as
with the Diamond-Blackfan syndrome. The research team was able to prove that the diseases caused by defective ribosomal proteins have a common molecular origin. And this mechanism leads to an accumulation of p53.

The p53 molecule is one of the most important factors in the body’s fight against excessive cell growth and the development of cancer. As so-called tumor suppressor gene, p53 can initiate various countermeasures when a cell divides uncontrollably – and ultimately it can even trigger their apoptosis. The paramount importance of this molecule is also illustrated by the fact that p53 is defective in circa half of all human tumors.

But the »guardian of the genome« also has its dark sides and can even cause diseases. This undesirable effect of p53 can evoke different symptoms. The respective effect depends in which cell type the tumor suppressor gene is activated. This also means that p53 serves as a kind of sensor to determine the functional ability of ribosomes. If they are defective it can trigger various symptoms depending on the cell type and kind of tissue.

In Diamond-Blackfan anemia this may occur via apoptosis of the cells in the bone marrow which produce blood cells. The new findings on the role of p53 in these disorders may lead to improved diagnosis and treatment of severe anemias.

Original Publication:
Nervous System

We study multifactorial diseases.
New Risk Gene Discovered for Restless Legs Syndrome

An international research team has succeeded in identifying PTPRD, a protein tyrosine phosphatase, as risk gene for RLS. Altogether, now four RLS genes have been discovered through genome-wide genetic studies. Carriers of risk sequence variants in these genes have a heightened risk of contracting RLS: Due to the known functions of the identified genes, RLS could be an early developmental disorder of the central nervous system.

Although RLS is one of the most common neurological disorders, it is still often not recognized or is falsely diagnosed. The Institutes of Human Genetics at Helmholtz Zentrum München and at Technische Universität München as well as at the Max Planck Institute of Psychiatry have been working for many years to expand knowledge about the underlying mechanism of RLS and to create an improved basis for diagnosis and therapy of the disease. Together with an international consortium, the Munich scientists studied a total of 2458 RLS patients and 4749 healthy test persons of the KORA population study.

Sequence variants (SNPs) were analyzed that were distributed over the whole genome. Upon comparison of the sequences between the patients and the control persons, variants in the PTPRD gene could be identified that are present in increased numbers in RLS patients, but appear less often in healthy test persons.

The gene name PTPRD stands for protein tyrosine phosphatase receptor type delta. The corresponding protein has been studied in the animal model and plays a role in the correct pathfinding of the neuron axons to the so-called motor neurons. These neurons regulate muscles directly or indirectly, for instance in the legs. Hence, PTPRD, just as the already identified RLS risk genes MEIS1, BTBD9 and LBCOR1, is important for the early embryonic development of the organism. This is
a further indication that RLS could be a very early developmental disorder of the central nervous system. The identified RLS risk genes enable for the first time targeted molecular genetic causal research of Restless Legs Syndrome and provide a basis for improving therapy.
Scientists of the research group of Prof. Dr. Magdalena Götz at Helmholtz Zentrum München and at Ludwig-Maximilians-Universität Munich discovered that reactive glial cells in the mouse brain can resume cell division following injury. These reactive glia cells become stem cells out of which, under favorable conditions in cell culture, neurons can form again. With this new discovery, the research group has thus succeeded in elucidating a further step to understanding the processes which can replace damaged brain cells after injury.

The scientists were able to show that normal star-shaped glial cells, the astrocytes, have the capacity to differentiate into neural stem cells following injury. They begin dividing again in the injured brain and even have typical stem cell characteristics. Although the astrocytes in the injured region of the brain only form new astrocytes, some of them under favorable conditions in cell culture can renew themselves and form neurons, oligodendrocytes and astrocytes – all main cell types of the central nervous system.

In their research the scientists could only observe the formation of new nerve cells in cell culture. Even if adult neural stem cells are transplanted into the brain, most of them only form glial cells. This means that there are strong in vivo signals from the surroundings that inhibit the formation of neurons in the adult brain. However, the research group led by Magdalena Götz was able to show that by introducing particularly strong signal molecules, cells can be stimulated to form neurons again – even locally in the injured region of the brain. Magdalena Götz, the stem cell expert, is investigating the molecular basis of brain development, especially in the cerebral cortex, and the mechanisms of the formation of neurons in the adult brain.
Regenerating Brain Cells

The research of Magdalena Götz casts doubt on one doctrine of neurobiology, namely the pure "support" role of glia. In earlier studies, Magdalena Götz discovered that glial cells in the brain can function as stem cells and that neurons are generated from these glial cells. She also showed which factors play a role in the cross-over from glial cells to neurons. The findings open up new avenues towards highly innovative therapeutic approaches by utilizing the endogenous glia for repair of degenerating neurons in the brain. In 2007 Magdalena Götz received the Gottfried Wilhelm Leibniz Prize, the highest scientific honor in Germany, for her research achievements.

The new findings provide decisive evidence that in an injured region of the brain, reactive glial cells possessing the potential of stem cells are present and thus can serve as source for new neurons. These results imply that the distant goal of being able to use these processes therapeutically is getting a little closer.
Genetic Defect Leads to Clouded Lens

At Helmholtz Zentrum München a genetic defect was deciphered which is responsible in mice for unusually small eyes and an incompletely formed, clouded lens. Conclusions can be drawn from these findings about cataracts in humans, because also in this case the lens body loses its transparency.

The ocular lens, which in the healthy eye is elastic and transparent, focuses light beams falling on the retina. Disorders in the differentiation of the lens fiber cells are involved in the development of cataracts, which often appear in the elderly.

The Aey12 mouse mutant, which the research team led by Prof. Dr. Jochen Graw at the Institute of Developmental Genetics discovered, is characterized by unusually small eyes, a microphthalmia. This malformation is also known in humans and almost always leads to blindness. It is often caused by atrophy or malformation of the eyeball. In the Aey12 mice, by contrast, the growth of the fibers that fill in the lens body are blocked. What remains is a cloudy and functionless lens vesicle.

As the scientists were able to show, the disease is caused by a defect in a gene that was previously unknown. The Neuherberg eye researchers gave the name Gjf1 to this gene responsible for the malformations of the Aey12 mouse mutants. It is a member of the connexin family. The genes belonging to this group contain the blueprint for the channel proteins, which form cell to cell connections. Such channels are of great importance for the exchange of substances between cells – including the exchange between the fiber cells of the developing ocular lens.

The scientists now speculate that through the newly discovered mutation, the structure of the Gjf1 channel protein is changed, and in this way the formation of the channel is hindered. Through this, however, the communication between the developing lens fibers would break down. As a consequence, signal molecules essential for the development of the lens could no longer be exchanged, or could only be exchanged to a limited extent. In this scenario, deficient cell communication would be the cause of the termination of fiber development – and ultimately, of the cloudiness of the eye lens, which would otherwise be transparent. This same phenomenon can also be
observed in human cataracts, a disease common in old age. In Germany alone more than half a million operations are carried out annually in which the cloudy and opaque lens is replaced with an implant.

From these findings on the genetic development of the ocular lens of the mouse, the researchers hope to better understand comparable genetic mutations in humans and to gain new insights into the origin of cataracts.
Anna-Lena Idzko (Institute of Radiation Protection) / Angelique Ne (Institute of Biological and Medical Imaging) / Thomas Jetzfellner (Institute of Biological and Medical Imaging) / Claudia Mayerhofer (Institute of Biological and Medical Imaging) / Saskia Björn (Institute of Biological and Medical Imaging)

The photo was taken on the Garching Heath north of the research campus of Helmholtz Zentrum München.
Focus Spanning

We are trying to find answers to the urgent problems of society.
Up to 20% of heart attack patients are affected by post heart attack depression. They have a significantly higher mortality rate than patients who do not suffer from stress, if the stress disorder is not treated. This is the result of a study on approximately 150 patients that had received an automatic cardioverter defibrillator (ICD) after a heart attack or cardiac arrest.

A team of scientists from Helmholtz Zentrum München, Technische Universität München and the German Heart Center showed that heart attack patients with posttraumatic stress disorder have a 3.5-fold higher mortality risk than patients without this diagnosis. In the study led by Prof. Karl-Heinz Ladwig the scientists observed 147 patients over a period of five years. They had survived a severe heart attack or sudden cardiac arrest, and they had received a pacemaker-sized automatic cardioverter defibrillator (ICD) implanted to prevent another cardiac arrest. The scientists asked detailed questions about symptoms which typically occur in posttraumatic stress disorder: anxious, intrusive memories of the life-threatening event, avoidance of behavior reminding them of the event as well as heightened nervous agitation or hypervigilance after the primary event.

A portion of the patients had elevated PTSD symptoms, and their lives were defined by recurring intrusive memories of their illness. They lived in a permanent state of anxiety and tenseness. These individuals exhibited a 3.5-fold higher mortality risk than patients who did not suffer from these symptoms and who were able to cope with their illness. How dramatic the survival gap actually is between cardiac patients with and without PTSD symptoms was also evident in the analysis of the absolute risks: Compared with 55 fatal events per 1000 person-years in patients without PTSD, the long-term absolute mortality risk accounted for 80 fatal events per 1000 person-years in patients with PTSD.
Other important factors influencing patients’ ability to survive after a heart attack were not associated with the risk of posttraumatic stress symptoms. Such risk factors include age, the ejection fraction as measure of the remaining myocardial contractility, or diabetes mellitus. Surprisingly, the researchers found no association with the presence of co-morbid depression and anxiety. The scientists concluded that the risk of PTSD is independent of the other above-named risk factors and cannot be explained by them.

The study is a contribution to improve cardiac patient care and long-term outcome. It shows that more attention should be dedicated to cardiac patients who exhibit PTSD symptoms to increase their survival rate.

Original Publication:
In Vivo Imaging of the Molecular Signatures of Lung Tumors

Vasilis Ntziachristos
Institute of Biological and Medical Imaging and Chair of Biological Imaging at Technische Universität München

Together with colleagues from Harvard Medical School and Massachusetts General Hospital in Boston, USA, Professor Vasilis Ntziachristos and his team have developed a new method capable of optimized fluorescence-tomographic imaging of tumors. Ntziachristos, who heads the Institute of Biological and Medical Imaging at Helmholtz Zentrum München and at Technische Universität München, and his team have developed a method which enables the use of so-called early-arriving photons in tomographic procedures.

Early-arriving photons are the first photons that arrive onto a photon detector after illumination of tissue by an ultra-short photon pulse and undergo less scattering in comparison to photons arriving at later times. Compared to continuous illumination measurements a combination of these less scattered photons with 360-degree illumination-detection resulted in sharper and more accurate images of mice under investigation.

With this technique, called early photon tomography (EPT), the scientists imaged lung tumors in living mice. For this purpose they injected a substance into the animals, which normally does not fluoresce, but becomes fluorescent after contact with certain cysteine proteases such as cathepsins. The amount of these proteases is enriched in lung tumors, which allows fluorescence imaging of the tumor tissue.

Comparison with conventional x-ray tomography showed that EPT is not only a very sensitive technique for imaging of lung tumors in living organisms, but also has the potential to reveal biochemical changes in neighboring tissue regions, which are caused by the tumor disease and which cannot be detected by conventional X-ray imaging.

Fluorescent molecules are useful aids in medicine and biology in order to track cellular and subcellular function such as gene expression, molecular pathways, protein concentration and function or metabolic processes. In conjunction with powerful new optical tomography techniques it offers new ways of looking into -omics fields through entire organisms in vivo.

Experimental arrangement of the early-arriving photons method: A pulsed laser emits ultra-short photon pulses, which hit the object of study and are scattered there. A special camera detects only the early-arriving photons to reduce the effects of photon scattering and reconstructs images of fluorescent contrast in vivo.
Making Disease Processes Visible

The new technique enables the imaging of tumors in living animals. The method results in sharper and more accurate images than traditional methods.

Hence, fluorescent techniques in combination with imaging diagnosis techniques allow the investigation of disease processes and tissue functions. However, a massive obstacle to the application of the technique in living organisms is the massive scattering of the light in biological tissue.

The German-American research group circumvented this problem by using an ultra-fast pulsed laser. Photons from such a source penetrate tissue and are only slightly scattered. The first photons to reach the detector are used for high-resolution imaging. At present EPT is practicable only with small animals. Further development of the equipment can allow applications of the technique also with larger organisms including humans.

Prof. Dr. Vasilis Ntziachristos

Since 2007 Director of the Institute of Biological and Medical Imaging, Helmholtz Zentrum München and Chair of Biological Imaging, Technische Universität München

Until 2007 Assistant Professor, Harvard University Medical School and Massachusetts General Hospital

2004 Top 100 of the World’s Best Innovators

Until 2001 Postdoc, Harvard University, graduate studies and PhD at the University of Pennsylvania

Original Publication:

Scientists of Helmholtz Zentrum München have succeeded for the first time in detecting the maximum possible number of chemical compounds out of carbon, oxygen and hydrogen in natural organic matter. This opens up new insights into the role of this widespread material in the global carbon cycle and thus for the world’s climate.

The maximal conceivable number of different chemical combinations of carbon, oxygen and hydrogen can be calculated mathematically. Using a new ultra-high-resolution mass spectrometer, scientists of the Institute of Ecological Chemistry at Helmholtz Zentrum München in collaboration with the Alfred Wegener Institute Bremerhaven and the Georgia Institute of Technology have succeeded in proving for the first time – not only theoretically but practically – that the maximum possible number of chemical compositions out of carbon, oxygen and hydrogen actually exists in natural organic matter (NOM). Little was known until now about NOM in the environment, but in fact it is present in considerable quantities in nearly all areas of the environment – in soil, sediment, fresh and salt water and in the air. It arises from the decomposition of organic substance and thus forms the link in the chain between the animate and inanimate environment. The new high-resolution analysis technique used at Helmholtz Zentrum München now enables considerably improved insight into the structural chemistry of this ubiquitous natural material. As study material the scientists chose a NOM fraction which is recognized and widely used in the scientific community as standard reference compound, the SuwFA, a fulvic acid fraction from the Suwannee River in the state of Georgia in the U.S. The FTICR mass spectrometer the scientists used was indeed able to detect all conceivable C-H-O compositions in the sample, proving that nature has in fact realized in NOM all mathematically possible chemical combinations.

The abbreviation FTICR stands for Fourier Transform Ion Cyclotron Resonance (mass spectrometer), which is distinguished by its extreme mass resolution and high mass accuracy.
Microorganisms degrade contaminants in groundwater preferably in gradient zones around contaminant plumes. Scientists of the Institute of Groundwater Ecology were now able to detect such degradation hot spots and the highly specialized microbial community established in them in an aquifer contaminated with tar oil.

The research team led by Dr. Tillmann Lüders and Dr. Christian Griebler investigated the spatial distribution of groundwater microorganisms in the contaminant plume underneath a former gas works site near Düsseldorf. Using high-resolution molecular biological and hydrogeochemical methods, they found a community of microorganisms specialized in the degradation of hydrocarbons in the gradient zone to the contaminant plume. This gradient zone in which tar oil components and sulfate as important electron acceptor mix harbors a high abundance of a previously unknown anaerobic toluene degrader, which could be identified based on its catabolic genes. This sulfate-reducing gradient zone, the researchers concluded, is a hot spot of microbial contaminant degradation.

The findings show that the distribution of microbial communities and degradation processes in contaminated aquifers are closely linked. They can therefore be used as a starting point for estimating the natural self-purification potential of groundwater, our most important drinking water resource.
Looking Ahead
We are pursuing a common scientific goal.
One Center, One Goal

Our goal is to become the world’s leading research center in the field of environmental health by 2013. To achieve this goal, we have successfully repositioned ourselves in the past three years and have refined the focus of our research, which is to investigate the complex interactions between health and the environment. In our endeavor to benefit society, we seek to close knowledge gaps and make a major contribution to improving patients’ health and quality of life.

The three POF programs »Systemic Analysis of Multifactorial Diseases«, »Environmental Health« and »Terrestrial Environment« provide an excellent framework for our research. We are focusing on developing individualized therapies for widespread diseases – in particular metabolic and respiratory diseases and disorders of the nervous and immune systems.

We are striving to elucidate the causes and mechanisms of diabetes mellitus by concentrating the national competence in this field at the Munich location. Beyond the planned federation of German diabetes centers, we will expand our capacity – together with the two Munich universities – by adding two new research institutes and two new clinical cooperation groups.

Based on the knowledge we have gained, we are endeavoring to make medical advancements in all of our core research areas, and are therefore continuing to expand translational research. Helmholtz Zentrum München is outstanding in basic research, and we are committed to advancing the ideas derived from it. Projects with potential for commercialization are being developed along the value chain for use in new therapeutic and diagnostic applications.

For the development of new active pharmaceutical ingredients (API), we need capabilities in the fields of chemistry and assay development at the Center. This is why we have launched an initiative for the Munich API center together with Technische Universität München. The new center for API research and profiling will assist both institutions in developing effective molecules and at the same time serve as platform for industrial cooperation with biotech and pharmaceutical companies.

Clinical trials are the crucial step in successful drug development: The scientific idea must be tried and tested in proof-of-concept studies. Clinical cooperation groups and translational centers with competent medical partners enable a constant exchange between clinical and basic research. Through this form of cooperation the Comprehensive Pneumology Center will make progress in the area of respiratory diseases and contribute with new insights to markedly improve health care.

Internationally competitive research needs excellent scientists. For that reason, the support of the young generation of scientists is of special importance to us. The Graduate Student Program will improve the training and supervision of our circa 300 PhD students and will increase the attractiveness of our research campus.
Successful Scientific Research Requires Dependable Structures

Scientists should have the freedom to focus entirely on their research, without having to worry about administrative matters. The responsibility of the administration is to create a conducive work environment and framework conditions so that Helmholtz Zentrum München scientists can attain their research objectives. From this shared motivation, the scientists and the administrative staff develop synergies, define roles and tasks, and use modern and competitive instruments.

With the optimization of our business processes we want to assist and support the core process: science. We have set in motion a structural reorganization at Helmholtz Zentrum München: We are creating lean and transparent decision-making structures, streamlining bureaucracy and are implementing decisions more quickly and effectively. In human resources development we are supporting the process of change and promoting an attractive work environment. Targeted business development is facilitating a faster and more efficient transfer of research results to applications. The development of a guiding principle for our center is creating an organizational culture oriented on common values and is strengthening the identification of our employees with Helmholtz Zentrum München.
Research in Three Strategic Programs

In 2008 Helmholtz Zentrum München applied for the second phase of program-oriented funding (POF II) of the Helmholtz Association with three strategic programs. Out of the six programs in the first phase of the funding (POF I), the Center developed three new strategic programs: »Environmental Health« and »Systemic Analysis of Multifactorial Diseases«, both in the research area of Health, and »Terrestrial Environment« in the area of Earth and the Environment. The programs result from the new strategic orientation of the center on the theme Environmental Health. The second phase of the program-oriented funding runs for five years, from January 2009 until December 2013.

The main emphasis of research in POF II is on disease: The focus in the program Environmental Health is primarily on lung diseases and reactions of the immune system to environmental diseases, for instance allergies and certain kinds of tumors. In »Systemic Analysis of Multifactorial Diseases«, diabetes and neurodegenerative diseases are the main focus. Cross-program projects in the areas of allergy, immunity and aerosol research represent interfaces between the program »Terrestrial Environment« and the area of health, in particular the program Environmental Health.

Systemic Analysis of Multifactorial Diseases

Multifactorial diseases have a great impact on the morbidity and mortality rates of a society. Important examples of multifactorial diseases are neurodegenerative diseases such as Parkinson’s and Alzheimer’s, metabolic diseases such as diabetes and hypertension, or autoimmune diseases such as rheumatoid arthritis. They arise from the complex interaction of an individual genotype with environmental and lifestyle factors.

»The next great challenge for research will be to elucidate how genetic factors contribute to the development of multifactorial diseases and to determine what prerequisites and environmental conditions are necessary for systemic diseases to arise. Our goal is to analyze the key genetic factors and biomolecular principles underlying multifactorial diseases.«

- Coordination: Helmholtz Zentrum München
- Program spokesperson: Martin Hrabé de Angelis
- Participating center: Helmholtz Zentrum München
Environmental Health

Environment-related diseases are among the great medical and socio-economic challenges for western society. The increasing life expectancy of the population and global changes in the environment will lead to a dramatic increase of diseases such as cardiovascular and respiratory diseases, cancer, allergies and diabetes, which develop from the complex interaction of environmental factors, lifestyle and individual genetic disposition. Research in the program »Environmental Health« shall contribute to a better understanding of this interaction, in order to develop better prevention and early detection strategies for chronic diseases and to undertake new approaches to therapy. Helmholtz Zentrum München and the Helmholtz Centre for Environmental Research in Leipzig are cooperating in the Environmental Health program.

»We are investigating how environmental factors and genetic disposition interact in the development of chronic diseases, and from this we shall develop individualized strategies for prevention, early diagnosis and therapy.«

Terrestrial Environment – Strategies for a Sustainable Response to Climate and Global Change

Terrestrial systems are the setting where human activities drive global change and where in turn humans are directly affected in their living conditions and economic development. That is why terrestrial systems are the crucial point of departure for developing and implementing strategies for sustainable development. Research in the Helmholtz program »Terrestrial Environment« shall safeguard the natural basis of human life and health while simultaneously providing and shaping options for social and economic development. The program is coordinated by the Helmholtz Centre for Environmental Research – UFZ, Leipzig and carried out by the Helmholtz centers in Leipzig, Jülich (FZJ) and Munich.

»The program »Terrestrial Environment« focuses on the idea of ecosystems services. The most important question we face today is how to utilize the components soil, water and plants for the benefit of humans.«
Helmholtz Zentrum München is developing a broad spectrum of new competitive technologies. In cooperation with an external commercialization partner and via industrial partners, the results of our research shall be transferred as quickly as possible into novel applications.

In 2008, circa 40 ideas for inventions generated 20 priority-based patent applications. The patent portfolio was refined with respect to the commercialization prospects of the patent families and aligned with the strategic reorientation of Helmholtz Zentrum München. Of 122 patent families, 58 are currently in active commercialization and 25 are earmarked for licensing and planned spin-offs. Altogether, a total of 79 out-licensing contracts have been concluded. Besides commercialization through patents, the Center was able to move forward with the commercialization of non-patented know-how – here in particular the sale and licensing of antibodies. In 2008 the costs for 122 patent families amounted to circa 916,000 euros.

### Spin-off Companies of Helmholtz Zentrum München

In recent years Helmholtz Zentrum München has generated 10 spin-off companies, which have a total of 350 employees. In the beginning of 2008 MedTherm GmbH was added, a spin-off company founded by Prof. Dr. Rolf Issels, head of the Clinical Cooperation Group »Hyperthermia« (together with Ludwig-Maximilians-Universität).

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Description</th>
<th>Date Founded</th>
<th>Key Technologies</th>
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<tbody>
<tr>
<td>ACTIVAERO GmbH (<a href="http://www.activaero.de">www.activaero.de</a>)</td>
<td>Founded under the name of Inamed GmbH in 1998 – since 2006 the medical device development division is Activaero GmbH – a competence center for inhalation technology and aerosol medicine</td>
<td>1998</td>
<td>Inhalation technology, aerosol medicine</td>
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<tr>
<td>Biomax Informatics AG (<a href="http://www.biomax.com">www.biomax.com</a>)</td>
<td>Founded in 1997 – develops software for the life science sector</td>
<td>1997</td>
<td>Software for the life science sector</td>
</tr>
<tr>
<td>Genomatix Software GmbH (<a href="http://www.genomatix.de">www.genomatix.de</a>)</td>
<td>Founded in 1997 – programs for elucidating mechanisms and pathways in biological systems</td>
<td>1997</td>
<td>Programs for elucidating mechanisms and pathways in biological systems</td>
</tr>
<tr>
<td>Inamed Research GmbH &amp; Co. KG (<a href="http://www.inamed.de">www.inamed.de</a>)</td>
<td>Studies on drug inhalation</td>
<td>1998</td>
<td>Studies on drug inhalation</td>
</tr>
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<td>Isodetect GmbH (<a href="http://www.isodetect.de">www.isodetect.de</a>)</td>
<td>Founded in 2005 – isotope analyses in the environmental sector</td>
<td>2005</td>
<td>Isotope analyses in the environmental sector</td>
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<td>Sirenade Pharmaceuticals AG (<a href="http://www.keyneurotek.de">www.keyneurotek.de</a>)</td>
<td>Taken over by KeyNeurotek AG in 2005 – focus on neurodegenerative diseases</td>
<td>2005</td>
<td>Neurodegenerative diseases</td>
</tr>
<tr>
<td>Vivacs GmbH (<a href="http://www.emergentbiosolutions.com">www.emergentbiosolutions.com</a>)</td>
<td>In 2005 taken over by Emergent BioSolutions including the rights to the vaccine vector technologies</td>
<td>2005</td>
<td>Vaccine vector technologies</td>
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The first therapeutic antibody made in Germany is based on immunological research conducted at Helmholtz Zentrum München (formerly GSF). The production method and the underlying effective principle of the antibody were developed, patented and out-licensed here in the mid-1990s. After successful conclusion of the clinical trials, the drug was developed to market maturity in the course of the last two years. Now, the European Medicines Agency EMEA has approved the antibody Catumaxomab for the treatment of malignant ascites. The drug shall be brought to market under the name Removab. It is the world’s first approved drug for the treatment of malignant ascites, an accumulation of fluid in the abdomen triggered by tumor diseases. Due to its trifunctionality, the antibody is able to effectively destroy scattered tumor cells. The drug will be marketed by Fresenius Biotech GmbH. The manufacturer is the partner company Trion Pharma GmbH, which was founded in 1998 as a spin-off of the present Helmholtz Zentrum München and today employs approximately 150 employees.

Hence, Helmholtz Zentrum München is the cradle of a new generation of immunotherapeutically active antibodies that can be targeted against cancer cells. The success story of the antibody is at the same time a confirmation of the technology transfer and translation model established at Helmholtz Zentrum München: Excellent basic research generates results with high application potential. The further development and ultimate transfer to clinical trials is facilitated by the close laboratory-hospital contact. Spin-offs and cooperations open up market potential and facilitate development to market maturity. The licensing and the final commercialization process are competently guided and supported by the Center and a partner technology company. The Center receives a share in the value creation and revenues from licensing the research results via the Life Science Foundation. The revenues flow back into the funding of innovative research projects. With this implementation strategy Helmholtz Zentrum München is involved in value creation in the biomedical sector. With the development of new therapies and innovative medicines, it is contributing — in line with the Helmholtz mission — to the solution of important social problems.
In 2008 there were 1956 employees at Helmholtz Zentrum München. 37% of their positions were financed by third-party funding. Circa half of the employees have fixed-term work contracts.

The majority of the staff works in the scientific area. Besides the technical staff there are 260 PhD students, 110 postdocs and 403 scientists employed primarily in the areas of biology, chemistry/biochemistry, physics and medicine. In 2008, as in other years, a wide array of apprenticeship positions was offered: Altogether 61 young people were being trained in the following professions: biology laboratory assistant, animal keeper, office administrator, radiation protection engineer, IT specialist, warehouse specialist, agricultural assistant, industrial mechanic and energy electronics specialist. The majority of the trainees received a regular work contract after successfully completing their training.

Equal Opportunity

The proportion of women scientists at Helmholtz Zentrum München increased between 2002 and 2008 (incl. postdocs and PhD students) from 37% to 47%. In grants for young scientists the proportion of women PhD students increased from 56% to 60%. For leadership positions the increase was even more striking – from 17% to 28%.

In 2008 Helmholtz Zentrum München joined the Munich Dual Career Office of Technische Universität München. The Dual Career Office supports women (and also men) in harmonizing career, mobility and family.

Human Resources Development and Further Training

Our Human Resources Development Office offers target-group-specific measures and promotes career paths in administration and science.

In 2008, 65 in-house further training events took place with 721 participants. The topics included modules on leadership and communication as well as training seminars on science topics and methodology. In addition, 547 employees attended external courses in order to receive specialized training.
**Distribution of staff by area of work**

1. Scientists  
2. Technical staff incl. infrastructure  
3. Administrative staff

---

**Scientists’ disciplines**

1. Biology/biotechnology/agricultural biology  
2. Chemistry/biochemistry  
3. Physics/biophysics  
4. Other disciplines  
5. Medicine  
6. Mathematics  
7. Engineering  
8. Informatics  
9. Geology/geophysics/geoeecology  
10. Veterinary medicine

---

**Vocational training disciplines**

1. Biology laboratory assistant  
2. Industrial mechanic  
3. Animal keeper  
4. Energy electronics specialist  
5. Office administrator  
6. IT specialist  
7. Warehouse specialist  
8. Agricultural assistant  
9. Radiation protection engineer
The financial volume of Helmholtz Zentrum München amounted to €197.9 million in 2008, of which €96.5 million came from institutional funding and €101.4 million from third-party funding. €32.8 million of this third-party funding was earmarked for supplementing the project-oriented research. The remaining third-party funds were remuneration for special tasks (operation of Asse Mine, evaluation of radiation dosimeters).

### Financial Development

The financial development of Helmholtz Zentrum München for the year 2008 is as follows:

#### Institutional funding 2008

<table>
<thead>
<tr>
<th>Category</th>
<th>Amount (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel costs</td>
<td>53.00 m</td>
</tr>
<tr>
<td>Material costs</td>
<td>22.96 m</td>
</tr>
<tr>
<td>Grants and subsidies to third parties</td>
<td>6.50 m</td>
</tr>
<tr>
<td>Ongoing investments</td>
<td>12.80 m</td>
</tr>
<tr>
<td>Construction/procurements &gt; € 2.5 m</td>
<td>1.21 m</td>
</tr>
</tbody>
</table>

Total: €96.47 m

#### Overall financing 2008

<table>
<thead>
<tr>
<th>Category</th>
<th>Amount (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel costs</td>
<td>78.00 m</td>
</tr>
<tr>
<td>Material costs</td>
<td>75.59 m</td>
</tr>
<tr>
<td>Grants and subsidies to third parties</td>
<td>10.70 m</td>
</tr>
<tr>
<td>Ongoing investments</td>
<td>32.37 m</td>
</tr>
<tr>
<td>Construction/procurements &gt; € 2.5 m</td>
<td>1.21 m</td>
</tr>
</tbody>
</table>

Total: €197.87 m
**Third-party revenues according to source**

### Research tasks

<table>
<thead>
<tr>
<th>Source</th>
<th>Total €</th>
</tr>
</thead>
<tbody>
<tr>
<td>Federal government project funding</td>
<td>12.8 m</td>
</tr>
<tr>
<td>State government project funding</td>
<td>0.2 m</td>
</tr>
<tr>
<td>German Research Foundation (DFG)</td>
<td>4.1 m</td>
</tr>
<tr>
<td>Industry (national)</td>
<td>1.5 m</td>
</tr>
<tr>
<td>Other (national)</td>
<td>4.1 m</td>
</tr>
<tr>
<td>EU</td>
<td>6.8 m</td>
</tr>
<tr>
<td>Other European institutions</td>
<td>0.0 m</td>
</tr>
<tr>
<td>Industry (international)</td>
<td>0.5 m</td>
</tr>
<tr>
<td>Other (international)</td>
<td>2.9 m</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>€32.8 m</strong></td>
</tr>
</tbody>
</table>

**as of: May 25, 2009**

### Special tasks

<table>
<thead>
<tr>
<th>Source</th>
<th>Total €</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asse Mine</td>
<td>60.5 m</td>
</tr>
<tr>
<td>Evaluation office</td>
<td>6.0 m</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>€66.5 m</strong></td>
</tr>
</tbody>
</table>

**as of: May 25, 2009**
Project Funding

Helmholtz Zentrum München demonstrates its competitiveness through its successful participation in grant competitions of the Federal Ministry of Education and Research, the European Research Framework Programme, the German Research Foundation, the Helmholtz Association of German Research Centres and other public and private institutions.

Altogether, in the area of project funding Helmholtz Zentrum München had 410 research contracts in 2008. With a subsidy of €6.8 million and at present 73 ongoing contracts, EU funding comprises the largest portion of international funds raised. In public funding for Helmholtz Zentrum München, EU grants take second place, comprising almost 21% of the finance volume, immediately after the project funding by the Federal Republic of Germany with 39% and ahead of funding by the German Research Foundation (DFG) with 12.5%.

Helmholtz Zentrum München has participated in more than 170 grant applications in the 7th Framework Programme (FP7) of the European Commission, of which 45 projects with EU funding amounting to more than €18 million were approved for the Center. With a grant of €1.6 million approved in 2008, Helmholtz Zentrum München is partner in the FP7 EMMA service infrastructure with the task of building up and coordinating a European infrastructure institution for phenotyping and archiving mammalian model genomes. The aim is to make mouse models for human diseases available to the biomedical research community.

Vasilis Ntziachristos, director of the Institute of Biological and Medical Imaging and professor of Biological Imaging at Technische Universität München, received the ERC Advanced Grant 2008 for his planned research on multispectral optoacoustic tomography. Within the framework of the tender of the Initiative and Networking Fund of the Helmholtz Association, the Center was allocated a university junior research group and funding for two spin-off initiatives. In 2008, through the Life Science Foundation, the Center applied for and was awarded projects on Chemical Biology with a financing volume of €1.65 million.

Helmholtz Zentrum München is participating in research programs of the Federal Ministry of Education and Research in the Competence Network for Radiation Research and in a joint study with the two Munich universities to investigate multimorbidity in over 65-year-olds, which is being funded with €2.6 million. In addition, the Center is a partner in the Competence Networks »Diabetes Mellitus« and »Adiposity«, for which it receives €1.6 million in funds.

Helmholtz Zentrum München is an important partner of the follow-up programs of the National Genome Research Network (NGFN), funded by the Federal Ministry of Education and Research: Together with other Helmholtz centers it is participating with more than 28% of the total funding in the NGFN-Plus tender and in 2 NGFN-Transfer projects. In 2008 Helmholtz Zentrum München was allocated €11.2 million in NGFN-Plus funding.
Importantly sources of funding for basic research at Helmholtz Zentrum München are the Deutsche Forschungsgemeinschaft (German Research Foundation — DFG) funding programs, which totaled €4.1 million in 2008. The Center is participating in coordinated programs to form «excellence clusters» with German universities and is taking part in Collaborative Research Centers (German abbreviation: SFB) and Transregional Collaborative Research Centers (Transregio).

The German Mouse Clinic has many national and international cooperation agreements, e.g. with the University of Oxford, Jackson Laboratories, the University of Utah, Massachusetts General Hospital Corporation, Kuamoto University, the University of Uppsala and the University of Helsinki. In other research areas cooperation agreements exist with the International Atomic Energy Agency (IAEA), the International Commission on Radiological Protection (ICRP), the U.S. Environmental Protection Agency (EPA), the National Institutes of Health (NIH), the Health Protection Agency and RIKEN Center for Developmental Biology in Japan and NACIS (Central Iron & Steel Research Institute).

In 2008 Helmholtz Zentrum München was engaged in circa 1400 international cooperations with universities, non-university research institutions and industrial partners in 59 countries throughout the world. These were a result of funding and cooperation agreements, bilateral exchanges between scientists during guest stays, and joint studies and publications. The U.S. and Canada are at the top of the list with respect to the number of international cooperation agreements. Within Europe, we cooperate mainly with partners in Great Britain, France, Italy, Austria, Switzerland, Belgium and the Netherlands. Outside of Europe and North America, we cooperate primarily with partners in Japan, Russia, and China.

<table>
<thead>
<tr>
<th>Funding program</th>
<th>Projects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual funding</td>
<td>36</td>
</tr>
<tr>
<td>Emmy Noether</td>
<td>2</td>
</tr>
<tr>
<td>EURLY Award</td>
<td>1</td>
</tr>
<tr>
<td>Leibniz Prize</td>
<td>1</td>
</tr>
<tr>
<td>Research groups</td>
<td>7</td>
</tr>
<tr>
<td>9 Priority programs</td>
<td>11</td>
</tr>
<tr>
<td>6 Collaborative Research Centers and 3 Transregios</td>
<td>31</td>
</tr>
</tbody>
</table>
Organizational Structure

Helmholtz Zentrum München – German Research Center for Environmental Health is a research institution of the Federal Republic of Germany and the Free State of Bavaria. It is a member of the Helmholtz Association of German Research Centres, the largest research organization in Germany with 28,000 employees and an annual budget of 2.8 billion euros. The Center has existed since 1960 and since 1964 under the legal form of a GmbH (German limited liability company).

The partners of Helmholtz Zentrum München are the Federal Republic of Germany, represented by the Federal Minister of Education and Research, and the Free State of Bavaria, represented by the Bavarian State Minister of Finance.

The bodies of Helmholtz Zentrum München are the Assembly of Partners, the Supervisory Board, the Board of Directors and the Scientific and Technical Board. By appointing members to the Supervisory Board, the scientific and technical staff is also involved in fundamental decisions of the Center. On scientific questions, Helmholtz Zentrum München also obtains the advice of the Scientific Advisory Board, which consists of external members.

Organizational Structure

Supervisory Board
The Supervisory Board monitors the legality, appropriateness and economic efficiency of the management. It makes decisions about general research objectives and fundamental research policy issues and financial matters, and lays down the basic principles for performance control.

MinDir Dr. Peter Lange
– Chair –
Head of the Department of Health, Biosciences and Sustainability, Federal Ministry of Education and Research

MinDirig Dr. Adalbert Weiß
– Vice Chair –
Bavarian State Ministry of Sciences, Research and the Arts

MinR Klaus Herzog
Bavarian State Ministry of Finance

MinDirig Dr. Karl Eugen Huthmacher
Federal Ministry for the Environment, Nature Conservation and Nuclear Safety

Dr. Arnd Kieser
Gene Vectors Department, Helmholtz Zentrum München

Prof. Dr. Peter Schröder
Microbe-Plant Interactions Department, Helmholtz Zentrum München

Prof. Ruth Brack-Werner
Institute of Virology, Helmholtz Zentrum München

RD Ulrich Schäffler
Federal Ministry of Education and Research

Dr. Martin Schölkopf
Federal Ministry of Health, Head of Division, Strategic Planning of Health Policy /Macroeconomic Aspects of Public Health Care
ORGANIZATIONAL STRUCTURE

Members of the Scientific Advisory Board

Advisory body to the Supervisory Board and the Board of Directors which evaluates the work of Helmholtz Zentrum München. The Scientific Advisory Board was constituted in 1994 with the purpose of carrying on an intensive discussion about the scientific programs and implementing an efficient result evaluation.

Members of the Scientific and Technical Board

As of: December 31, 2008

Prof. Dr. Nikolaus Blum
CFO

Prof. Dr. Martin H. Gerzabek
Department of Forest and Soil Sciences, Institute of Soil Research, University of Natural Resources and Applied Life Sciences, Vienna

Prof. Dr. Wolfgang-Ulrich Müller
Institute of Medical Radiation Biology, University Hospital Essen

Prof. Dr. Dierk Scheel
Department of Stress and Developmental Biology, Leibniz Institute of Plant Biochemistry

Prof. Dr. Sylvia Schnell
Institute of Applied Microbiology, University of Giessen

Members of the Board of Directors

The Board Members are the legal representatives of Helmholtz Zentrum München. They conduct business according to the Partnership Agreement, the resolutions of the Assembly of Partners and the Supervisory Board.
Research Institutes and Departments

and joint appointments with Ludwig-Maximilians-Universität München (LMU) and Technische Universität München (TUM)
The Helmholtz Association

The Helmholtz Association of German Research Centres is the largest scientific organization in Germany. Sixteen scientific-technical and biological-medical research centers have joined together to make substantial contributions to basic scientific issues. With its staff of internationally renowned scientists, the Helmholtz Association is using its potential to take an internationally leading position in all of its research areas to investigate complex scientific, social and economic issues with a holistic approach and to offer appropriate solutions to identify solutions, working from the base up and translating them into applications to develop methods, technologies and services and to advise both policy-makers and society to contribute significantly to the effectiveness and appeal of the entire scientific system in Germany.