HelmholtzZentrum münchen
German Research Center for Environmental Health

2010
Annual Report

50 years
Helmholtz Zentrum München

Helmholtz Zentrum München –
German Research Center for Environmental Health

At a glance:

3	research programs as part of the program-oriented funding (POF) framework of the Helmholtz Association of German Research Centres
975	publications in international journals (2010)
131	patent families
14	spin-offs and joint ventures
1 879	employees (2010)
46	trainee positions
33	independent institutes and research units
8	junior research groups
14	clinical cooperation groups
5	cooperations with German Health Research Centres
6	grants from the European Research Council (ERC)
173	million euros total financial volume (2010)
52	hectare research campus to the north of Munich

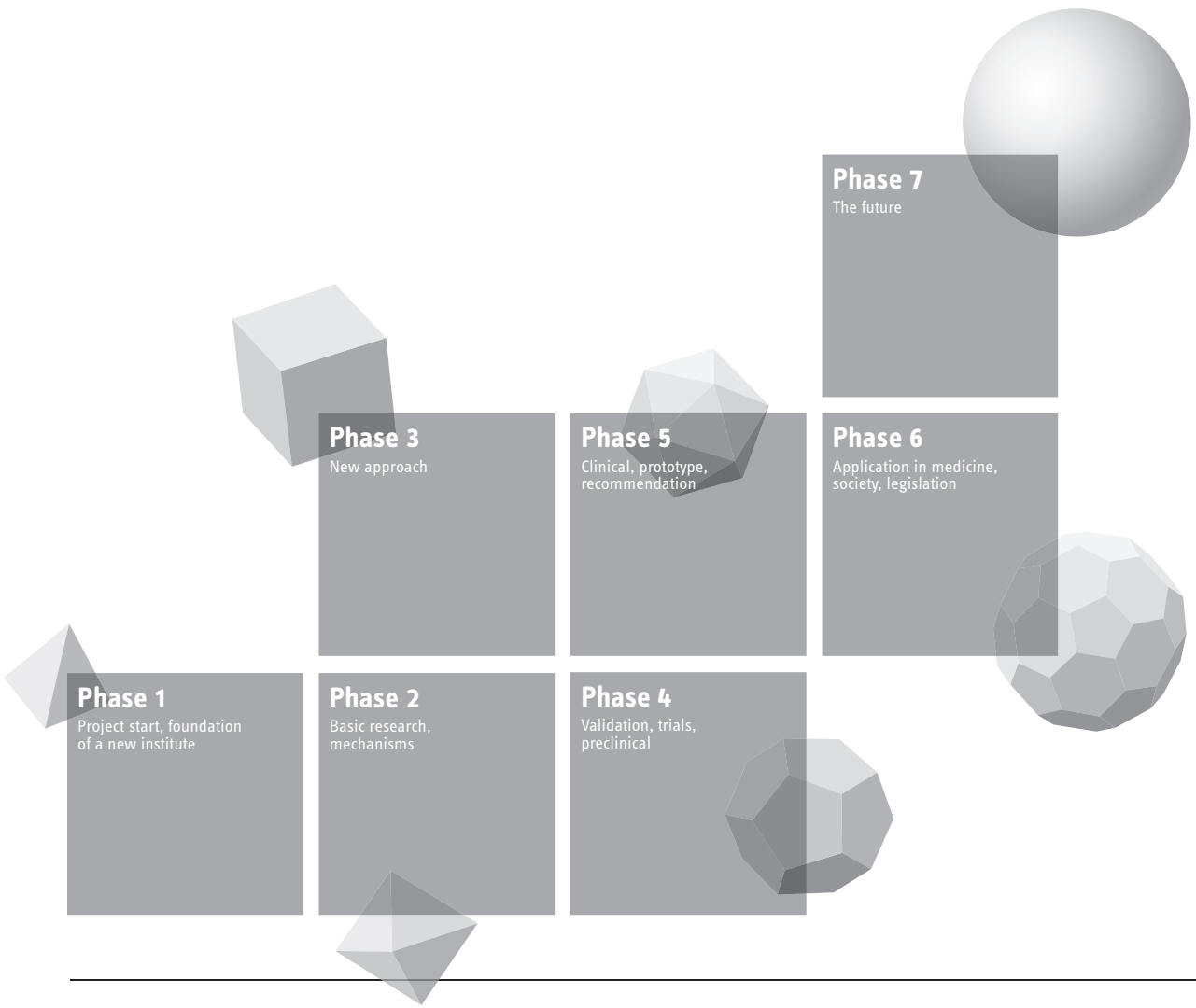
Helmholtz Zentrum München is a member of the largest scientific organization in Germany:
The Helmholtz Association of German Research Centres has 31,000 employees in 17 research centers and an annual budget of around 3.3 billion euros. It pursues long-term research goals on behalf of the state and society. Its results contribute to preserving and improving the foundations of human life.

HelmholtzZentrum münchen
German Research Center for Environmental Health

Annual Report 2010

Infographics

Based on the title of our annual report, “Transforming Health Research”, these infographics depict not just the chronology but also the development of a project, from its inception to its application in society, i. e. its benefits. The milestones on this path provide us with a vision of the future – a vision of where research may be in the years and decades to come.



Transformation

2010
Annual Report

50 years
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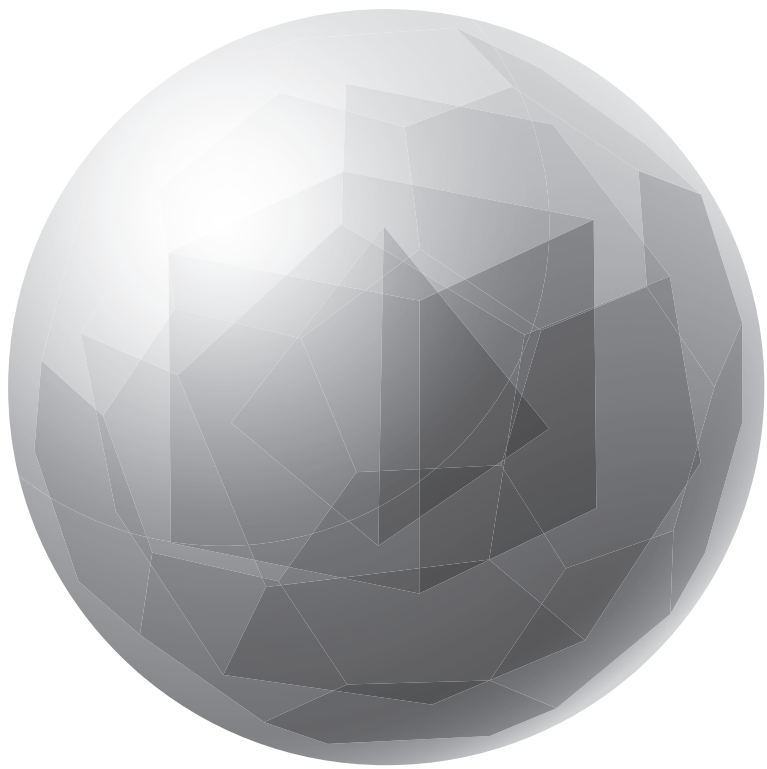


The term “transformation” is derived from the Latin word “transformare”, to change, and denotes a change in form or structure. Helmholtz Zentrum München itself is the result of an extensive transformation process spanning 50 years. The title of this annual report, “Transforming Health Research”, addresses the process of transformation at three levels:

- Health research at the Center, its development in the last 50 years and a look to the future
- The demands of society on health research
- Research, which uses known results to ask new questions and thus produces new knowledge.

In this sense, research at the Center is the initiator, means and object of this transformation: It transforms ignorance into knowledge with the objective of achieving a clear benefit for society. In the process, all projects undergo several phases – which are depicted by seven different bodies, from a pyramid to a sphere. On the cover, these shapes merge into one holographic body, thus symbolizing the continuous transformation of the Center and its research.

The inside pages are structured by means of graphics, depicting the various aspects of the transformation of past and future key research topics at the Center.

Helmholtz Zentrum München

Transformation through Five Decades of Research

Transforming Health Research

Key data spanning five decades reveal the successful transformation of important research topics at Helmholtz Zentrum München.

Diseases through the Ages

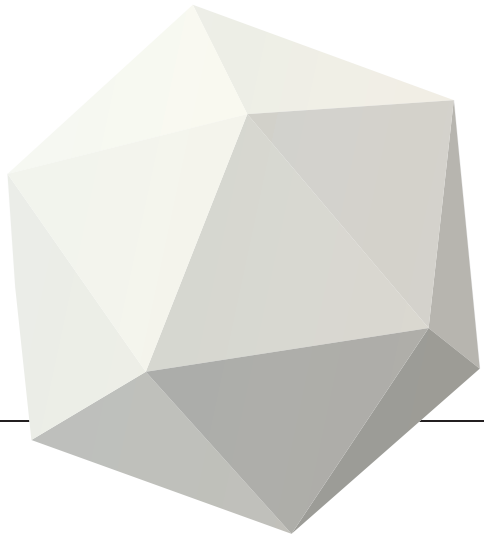
The meaning of individual diseases for the morbidity and mortality of society is changing. Helmholtz Zentrum München focuses its research on common diseases that will shape the future of our society.

Successful Research at the Center

Exemplary successes reveal the transformation process of research topics and their further development.

Research Topics and Current Research Highlights

Within the main topic “Environmental Health”, Helmholtz Zentrum München focuses on researching metabolic diseases and lung diseases and contributes to research into neuropsychiatric disorders, infections and immunological diseases as well as cardiovascular diseases.



Transforming Health Research

50 years
Helmholtz Zentrum München

Diseases through the Ages

The most frequent causes of death – from 1990 to 2030

Therapy

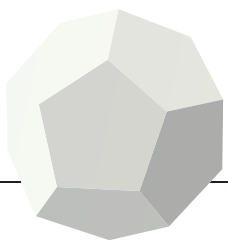
From research to successful application:
Antibodies against cancer

Diagnosis

From research to successful application:
More mathematics for better radiation protection in x-ray diagnostics

Prevention

From research to successful application:
Precise calculation of exposure to radiation on flight paths



Metabolic Research

at Helmholtz Zentrum München since 1960

Neuropsychiatric Research

at Helmholtz Zentrum München since 1960

Lung Research

at Helmholtz Zentrum München since 1960

Infection and Immunology Research

at Helmholtz Zentrum München since 1960

Cardiovascular Research

at Helmholtz Zentrum München since 1960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24–37


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46–59


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84–91


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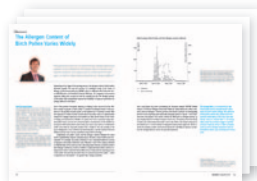
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152–165


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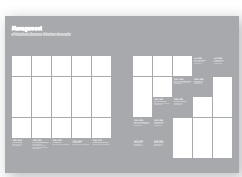
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Transforming Health Research

Transforming Health Research

Leading the Center into the future: Prof. Dr. Günther Wess (right), CEO and President, and Dr. Nikolaus Blum, CFO

2010 was a successful year for Helmholtz Zentrum München: In terms of its number of publications and its success in raising third-party funds, the Center has already reached its goal formulated in one[2013], which is to become the world leader in Environmental Health by 2013. In terms of third-party funds, being awarded four Starting Grants by the European Research Council is a particular success and underlines the research center's excellence and sustainability.

2010 was an important year for the development of Helmholtz Zentrum München. The Center's number of publications has increased once again; compared to 2005, it has doubled, while the sum of impact factors has even tripled. In 2010 scientists of Helmholtz Zentrum München published 975 articles in renowned scientific trade journals. 112 publications appeared in journals with an impact factor greater than ten. The overall impact factor stands at 5750 points. Success in raising third-party funds is another indicator that the strategy of Helmholtz Zentrum München is bearing fruit. However, 2010 was also a year of taking stock, prompted by anniversaries at Helmholtz Zentrum München. The Center celebrated its 50th anniversary, the research platform for population-based health surveys, KORA, was able to look back on 25 years of health research, and the Institute of Epidemiology was able to review 20 years of research on environmental health.

Compared to 2005, the Center's number of publications has doubled, while the sum of impact factors has even tripled.

Our current Center, the former Gesellschaft für Strahlenforschung (GSF, Society for Radiation Research), is the result of an extensive transformation process. After several name changes, most recently at the end of 2007, we are now the "Helmholtz Zentrum München – German Research Center for Environmental Health". Some of the reasons for this profound transformation were growing competition by specialized and more focused research organizations, the faster pace of innovation, and greater competition for the distribution of research funds. It was therefore deemed necessary to find solutions for these challenges: our strategy was restated, and our research was given a new structure. This ensured all necessary steps were taken to remain competitive, thus allowing for sustainable growth. Today, Helmholtz Zentrum München dedicates itself to the future of medicine in the field of health research and has created the necessary prerequisites for growth – not least of all through partnerships.

In recent years we have devised goals and criteria for our new direction under the motto one^{2013}: It describes our goal to become the world's leading research center in the field of environmental health. However, the successful implementation of one^{2013} requires joint efforts – one research center with a common focus, a common goal, and a common strategy. A key factor in this process is the translation of science into benefits for the general public, at above-average success rates, and to serve society. A powerful example of this is Prof. Dr. Magdalena Götz, Director of the Institute of Stem Cell Research, who received the Order of Merit of the Federal Republic of Germany on 25th June 2010 for her achievements in researching the molecular fundamentals of brain development.

Successful translational research, which transforms science into patients benefits, is not just part of our own endeavors and of the Helmholtz mission, but also a key demand of the Federal Ministry of Education and Research (BMBF) on the German Centres for Health Research. Therefore, clinicians from universities and researchers from non-university institutions work together in these centres. The German Centres for Health Research underpin the focus of the German Government's health research

strategy on common diseases and its intention to stimulate the rigid structures of the research landscape.

- The Centres for Neurodegenerative Diseases and Diabetes are already in existence and are developing very well. Helmholtz Zentrum München is involved in both, and the office of the German Centre for Diabetes Research (DZD) is located at Helmholtz Zentrum München. Important steps in expanding our diabetes research in 2010 were the foundation ceremony of the DZD on 9th November in Berlin, and the successful appointment of Prof. Dr. Anette-Gabriele Ziegler as Director of the Institute of Type 1 Diabetes Research at Helmholtz Zentrum München, effective 15th March 2010. The W3 professorship of Prof. Dr. Ziegler is sponsored by the Initiative and Networking Fund of the Helmholtz Association. Furthermore, she is a tenured professor of Diabetes and Gestational Diabetes at Technische Universität München.

- Further German Centres for Lung Research, Infection Research, Cardiovascular Research and Cancer Research were evaluated in autumn 2010. The Munich research institutions have pooled their resources and competences in these areas, with Helmholtz Zentrum München being involved in lung research, cardiovascular research and infection research. In our translational Comprehensive Pneumology Center (CPC), which was opened up in 2010 by Federal Minister Prof. Dr. Annette Schavan and Minister of State Dr. Wolfgang Heubisch, Ludwig-Maximilians-Universtität Munich (LMU), the university's hospital, and the Asklepios Pulmonary Hospital Gauting have pooled their resources in the field of lung disease research. Furthermore, Helmholtz Zentrum München and the universities in Munich are actively involved in the Munich Heart Alliance and the Center for Infection Medicine Munich. These networks have laid the foundations for successful evaluations in the autumn.

Together with the Munich universities, Helmholtz Zentrum München is involved in five of the six new German Centres for Health Research.

Helmholtz Zentrum München is the only Helmholtz Center that is involved in five of the six new Centres for Health Research. This shows that our focus on environmental health is perfectly in line with the concept of the German Government, enabling us to make excellent contributions to researching the most common diseases. However, this also illustrates the importance of our Center's clear focus on diabetes mellitus and chronic lung diseases as well as concrete patient benefits. Thus we contribute to overcoming interdisciplinary limitations and work jointly towards the goal of effectively reducing the suffering caused by the most common diseases.

As a step towards reaching this goal, the Center reinforced its epidemiological expertise in 2010. Under the leadership of Prof. Dr. Annette Peters, an internationally renowned epidemiologist, the new Institute of Epidemiology II will investigate how environmental factors affect health at population level. At the same time technologies and theoretical foundations, which are critical for large population surveys, are developed further through the appointments of Prof. Dr. Thomas Illig as head of the new Research Unit Molecular Epidemiology, and Prof. Dr. Konstantin Strauch at the newly founded Institute of Genetic Epidemiology.

This expertise allows us to successfully work on and further develop our focus on environmental health. Every person reacts differently to environmental influences

and lifestyle factors – therefore the future will bring a continuous decrease in generally valid, standardized therapies. The population-based surveys, conducted by us through KORA and in future also in connection with the national cohort, form one of the foundations of personalized medicine and thus the path towards more effectiveness, more safety and more efficiency in health care. Helmholtz Zentrum München has proven that it can make key contributions towards progress on the path to personalized medicine and thus to measurable patient benefits. At the Munich excellence cluster "m⁴ – A new dimension in drug development", Helmholtz Zentrum München is, for example, involved in epidemiological projects, but also in projects for the development of new therapies for lung disease, cardiovascular diseases and infectious diseases.

Helmholtz Zentrum München has proven that it can make significant contributions to measurable patient benefits.

Chemical biology is another area that aims to create added value from research. This discipline describes the knowledge required to manipulate biological processes with chemical molecules – be it to investigate the processes in basic research thoroughly or to develop new therapies and active ingredients. In 2010 we were able to establish the Assay Development Platform and the new junior research group Systems Biology of Small Molecules. The Munich Center for Drug Research and Profiling, which is being established in conjunction with Technische Universität München, will benefit from both units. Skills such as metabolomics and chemical biology create competencies that allow us to cooperate with industry on an equal footing. In this respect, too, the Center is on the right track: In addition to the industry cooperation stipulated in the excellence cluster, individual contracts for drug development were signed in 2010, both with Roche Diagnostics and with Boehringer Ingelheim.

However, the medicine of the future requires even more than that. It needs scientists who rise to the challenge of contributing to the foundations of medical progress. In 2010 Helmholtz Zentrum München, together with both Munich universities, founded the Helmholtz Graduate School of Environmental Health (HELENA) and the Helmholtz Research School "Lung Biology and Disease". HELENA offers structured and application-oriented training with support at three levels: the junior scientists receive extensive guidance and mentoring from a Thesis Committee, the Graduate Student Office and a confidant for doctoral students. And HELENA also breaks the mold in terms of its specialist areas: the Graduate School trains students in the eight thematic fields that are of crucial importance in order to be able to understand and research genetics and environmental factors and their influence on the most common diseases. HELENA is the world's first graduate school focused on environmental health.

Change, extensive networking, and new structures in associations require effective management. Our governance structure, introduced in 2009, has established the principle of joint decision-making. In 2010 this structure proved that it meets the special requirements of a research institution: The Scientific Review Committee regularly discusses a wide range of scientific advances. This ensures the perpetuation of initiated change processes and scientific successes. In addition to joint decision-making, the ability to react quickly, thus eliminating obstacles to implementation, is another important goal of the new management structure. For that purpose decentralized units are being set up with autonomous decision making-powers regarding employees and finances – within the limits of an agreed budgets. In future

the institutes and research units located at Großhadern will be looked after locally by the new office, which was established in 2010. In the scientific arena, effective structures are being created by the merger of scientific institutes and research units that work in related fields, to create departments. The precursor to this is the Center's 50-year competence in the field of radiation research: the first department of Helmholtz Zentrum München is the Department of Radiation Sciences, which was founded on 23 November 2010.

HELENA is the world's first graduate school focused on environmental health.

The results achieved in 2010, but also during the last 50 years, are based on cooperation. Helmholtz Zentrum München is the result of continuous change, and the key to any process of change are the people involved in it. Only employees who accept and support change can make a vision come to life. A good mix of experienced and young employees enabled our Center to develop its own, strong dynamics in recent months. Hence we are on the way to our own, new identity. We would like to use this opportunity to thank all our employees for their great dedication.

We are grateful to the Supervisory Board and the Scientific Advisory Board for supporting our activities, to the Federal Ministry of Education and Research and the Bavarian state government for providing funding and to the President and Central Office of the Helmholtz Association for their support.

The successes of the year 2010 illustrate that science only works in a continuous process of change, of transformation. For that reason the main focus of this annual report will be on transformation. In light of the occasion we will not only provide you with a selection of excellent scientific results achieved in 2010, but also in the last 50 years. They illustrate that Helmholtz Zentrum München has been conducting successful research in the field of environmental health for 50 years now: the joint effects of genetics and environmental influences on the development of common diseases have been a research topic as long as our Center has been in existence. For that reason our annual report for this year focuses on "Transforming Health Research".

Prof. Dr. Günther Wess
CEO and President

Dr. Nikolaus Blum
CFO

1

1 Neuherberg around 1925: Our campus timeline starts on page 184 with a look at past history.
2 The campus in 2011: The research campus of Helmholtz Zentrum München, photographed in easterly direction

2

50 Years

of Helmholtz Zentrum München

2000
Using the mouse mutant Beethoven, researchers at the Center develop a model for investigating age-related deafness

2001
Under the umbrella of the KORA project, the diabetes family survey starts with 1800 participants

2002
The Center's spin-off Inamed launches the inhalation system AKITA

2003
First evidence of the effects of fine particles on the risk of myocardial infarction

2004
Scientists of the Center act as advisors for the transposition of radon risk levels into precautionary levels

1990
Research into the effects of indoor chemicals, inter alia on the nervous system, leads to stricter statutory regulations

1991
The Institute of Molecular Virology researches the role of retroviruses in tumors

1992
Development of a patient chipcard for diabetics

1993
Foundation of the Institute of Inhalation Biology, precursor of the Institute of Lung Biology and Disease

1994
The Center presents the world's first homogenous data sets for radiation exposure of aircrews

1980
The Institute of Medical Informatics and Systems Research researches social variables and cardiovascular risk factors as part of the Munich Blood Pressure Study

1981
Foundation of the Service Unit Monoclonal Antibodies at the Institute of Immunology as a precursor of the Service Platform for Antibodies

1982
Decommissioning of the research reactor Neuherberg

1983
Foundation of the interdisciplinary Munich Air Pollution Research Network (MAGL) in cooperation with both Munich universities

1984
The Institute of Medical Informatics and Systems Research conducts research for improved treatment of diabetics

1970
Physical fundamentals for the application of lasers to medical problems

1971
Scientists at Neuherberg shape the new field of environmental chemistry and establish procedures for the prediction and evaluation of the environmental behavior of substances

1972
The Department of Coherent Optics investigates eye damage through laser radiation

1973
The Institute of Pathology discovers virus-like particles in radiation-induced osteosarcomas

1974
The Department of Genetics achieves an evaluation of the risk posed by chemical mutagens

1960
Foundation of Helmholtz Zentrum München

1961
The research center has 60 employees – among them 18 scientists in two institutes

1962
The 100th radiation protection course is held

1963

1964
Research into lung damage by breakdown products of radon

2010

50 years
Helmholtz Zentrum München

2005
The Institute of Stem Cell Research identifies molecular mechanisms of nerve regeneration in the adult brain

2006
Center develops inhalative vaccination strategies

2007
Mouse model for the loss of function in beta cells during the development of diabetes

2008
KORA-AGE takes up research into myocardial infarctions, strokes, and diabetes in old age

2009
The Center's spin-off TRION Pharma receives approval by the European Medicines Agency EMEA for an antibody effective against cancer cells, based on immunological research at the Center. The antibody is based on immunological research at the Center.

1995
Based on the Vaccinia Virus, the Institute of Molecular Virology develops a vector system for creating vaccines

1996
Based on MONICA, studies in Cooperative Health Research (KORA) begin in Augsburg

1997
Center starts research into the consequences of diabetes mellitus with over 1000 participants

1998
Spin-off of Trion Pharma GmbH with the aim of further developing a family of antibodies for tumor therapy

1999
The Genome Analysis Center begins its analysis of gene markers relevant to metabolic disorders

1985
In Augsburg the studies conducted for the international study "Monitoring of Trends and Determinants of Cardiovascular Disease" (MONICA) by the World Health Organization (WHO) begin

1986
The Institute of Radiation Protection develops the first voxelphantoms for radiation protection in the medical and professional field

1987
Redevelopment of a concept for health research

1988
The Institute of Immunology starts working with recombinant antibody technology and the production and preclinical trial of bispecific antibodies

1989
Evaluation of expert systems for the support of therapies in the treatment of diabetes

1975
First successful bone marrow transplant in Germany

1976
Concept of the equivalent dose for the description of the radiation risk at low doses

1977
Worldwide first clinical application of T-cell depletion for weakening the immune reaction

1978
The disposal of radioactive waste in the Asse Mine ends

1979
Procedures for the removal of leukemia cells from bone marrow allow for autologous bone marrow transplants

1965

1966
First steps to research allogenic bone marrow transplants for the treatment of leukemia patients

1967
The disposal of radioactive waste in the Asse Mine pit begins on a trial basis

1968
Research into the absorption and distribution of particles in the lung as part of aerosol research

1969
The newly established research group Data Processing in Medical Diagnostics analyzes possibilities for an automated EEG analysis

Timeline 2010


3


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January

1. Center hosts Humboldt awardee: The well-known Australian structural biologist Prof. Gottfried Otting conducts research at the Center for six months. — 1

11. Gene variants promote atrial fibrillation: As part of an international cooperative project, researchers at the Center discover gene variants that make changes in the cardiac rhythm likely.

22. Junior management training at the Center: The first graduates of the six-month online training course "Effective Managing and Performing" receive their certificates.

26. Amongst winners: In the leading-edge cluster competition of the Federal Ministry of Education and Research, the Munich Initiative m⁴, which researches new approaches to personalized medicine, was one of five winners of the competition. — 2


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February

2. Foundation: With the Pettenkofer School of Public Health, Ludwig-Maximilians-Universität, Helmholtz Zentrum München and the Bavarian Office of Health and Food Safety promote research and training in the health sciences.

24. Change of name: Bearing the new name "Sozialwerk am Helmholtz Zentrum München", the self-help organization set up in 1999 will continue to support employees, arrange sports activities, and support child care at the Center.

26. AtemWeg supports research into lung diseases: Helmholtz Zentrum München and Münchner Bank eG announce the establishment of the "AtemWeg" foundation for researching lung diseases. — 3

28. Leading German human geneticists at the Center: According to the trade journal "Laborjournal", Prof. Dr. Dr. H.-Erich Wichmann, Institute of Epidemiology, Prof. Dr. Thomas Meitinger, Institute of Human Genetics, and Prof. Dr. Thomas Illig, Research Unit Molecular Epidemiology, are ranked among the ten most frequently cited human geneticists in the German-speaking world.

March

1. Allergy Center under new management: Prof. Dr. Carsten Schmidt-Weber assumes leadership of the Allergy and Environment Center (ZAUM), supported jointly by Helmholtz Zentrum München and Technische Universität München.

10. Metabolomics in life sciences: The Munich Functional Metabolomics Initiative, Helmholtz Zentrum München and Technische Universität München host the first international Metabolomics Symposium in Germany. — 4

11. 40 years plant fire brigade: During its annual general meeting the plant fire brigade at Helmholtz Zentrum München and its 32 active members look to the future optimistically. — 5

5

13. New chairman for the Supervisory Board: Bärbel Brumme-Bothe, director of the department "Life Sciences – Research for Health" at the Federal Ministry for Education and Research, succeeds Dr. Peter Lange as chairman of the Center's Supervisory Board. — 6

1. Epidemiological research extended: The newly established Institute of Epidemiology II, led by Prof. Dr. Annette Peters, researches the effects of air pollutants on health and their correlation with chronic diseases.

3. Assay Development and Screening Platform launched: Under the leadership of Dr. Kamyar Hadian, the new platform develops cell-based biochemical test systems for substance screening.

4. Lung ambassadors introduced: Together with the AtemWeg foundation, soprano Nadja Michael and actress Lisa Martinek campaign for increased research into lung diseases.

March

15. Focus on disease patterns extended: The newly established Institute of Diabetes Research, led by Prof. Dr. Anette-Gabriele Ziegler, researches type 1 diabetes mellitus and gestational diabetes. — 7

30. Top ranking in non-clinical neurosciences: According to the trade journal "Laborjournal", Prof. Dr. Magdalena Götz, Director of the Institute of Stem Cell Research, is ranked among the most frequently cited German-speaking neuroscientists.

April

7. Gene for birth weight and diabetes risk: Pan-European study discovers genetic component for a correlation between low birth weight and a later risk of type 2 diabetes.

11. International study confirms predisposition for kidney diseases: Researchers hope for new insights to elucidate functional disorders.

22. Excellent promotion of young scientists: In cooperation with Ludwig-Maximilians-Universität and Technische Universität München, the Center establishes the first "Helmholtz Graduate School for Environmental Health" (HELENA).

May

10. Prelude at the Center: An international group of science attachés starts its fact-finding mission to Munich as a research location at the Neuherberg campus. — 8

18. Hosting a minister: Possibilities of linking basic research and clinical research take center stage at the visit of the French Research Minister Valérie Pécresse. — 9

31. Important element of doctoral education: Focusing on eight thematic fields, the lecture series "Environmental Health" imparts key foundations of environmental health research.

10

13

8. Strengthening cooperation: The Canadian Deputy Minister of Advanced Education, Dr. Annette Trimbee, and her delegation gather information on new joint projects. — 10

25. Geographic approaches to epidemiology and health care: 80 participants attend the first workshop of the Center's newly established working group "Health Geography" by the German Society for Epidemiology (DGEpi).

28. Development of allergies and standardization of biobanks: The Center is involved in two new projects, which are supported by the European Union as part of the Seventh Framework Program for Research (FP7).

7. Implementing research results quickly: At the Center for Infection Medicine Munich (ZIMM), Ludwig-Maximilians-Universität, Technische Universität München and Helmholtz Zentrum München join forces against infections.

12. Translational Research Center unveiled: Prof. Dr. Annette Schavan, Federal Minister of Education and Research, and the Bavarian Science Minister, Dr. Wolfgang Heubisch, open up the Comprehensive Pneumology Center (CPC). — 13

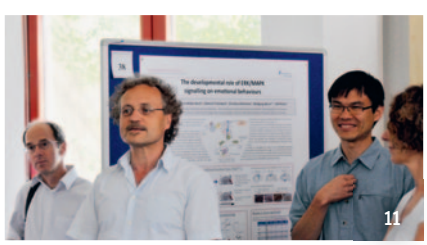
13. New nomenclature for leucocytes: An international committee led by Prof. Dr. Loems Ziegler-Heitbrock updates the official nomenclature for white blood cells.

June

25. Molecular fundamentals of brain development researched: Prof. Dr. Magdalena Götz, Director of the Institute of Stem Cell Research at Helmholtz Zentrum München and tenured professor at the Physiological Institute at Ludwig-Maximilians-Universität Munich, receives the Order of Merit of the Federal Republic of Germany.

29. Promoting cooperation on campus: The event series "Treffpunkt Wissenschaft" brings together working groups from different programs. — 11

30. Awards for communications media: The Center's staff magazine is awarded a Best of Corporate Publishing Award, the Annual Report receives an international Communication Design Award. — 12



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BEST CP PREISTRÄGER 2010 BCP BEST OF CORPORATE PUBLISHING

12

July

26. Three ERC Starting Grants for researchers at the Center: Prof. Dr. Matthias Heikenwälder, Institute of Virology, Dr. Dr. Melanie Königshoff, Institute of Lung Biology, and Dr. Daniel Razansky, Institute of Biological and Medical Imaging, receive funds totaling 4 million euros from the European Research Council.

29. Pooling competencies for Munich research into heart diseases: Ludwig-Maximilians-Universität, Technische Universität München, Helmholtz Zentrum München, and Max-Planck-Institute of Biochemistry jointly set up the Munich Heart Alliance.


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1. Point of attack against neurodegenerative diseases: The Michael J. Fox Foundation funds a project of the Center aimed at determining the structure of a protein central to the development of Parkinson's disease.

2. Systematically exchanging genes: Researchers at the Center describe ways of altering genes directly in the ovocytes of a mouse.

9. Center coordinates new EU project: Evaluating the cancer risk at low radiation doses by combining epidemiological and radiobiological approaches is the goal of the EpiRadBio project, for which the Center cooperates with 16 partners from nine European countries.

9. On the trail of inflammatory processes: In order to investigate inflammatory tissue structures, the Center sets up a new junior research group under the leadership of Prof. Dr. Mathias Heikenwälder.

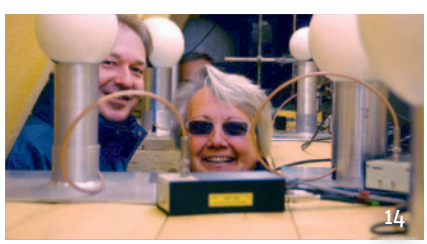
1. Researching systems biology of small molecules: Under the leadership of Dr. Monica Campillos Gonzáles, the new junior research group takes up its work.

10. Protein structure as cover page: Researchers at the Center and at Technische Universität München elucidate the structure of a signal protein region that appears on the cover of the Journal of Biological Chemistry.

23. Allergies and asthma develop separately: An international meta study involving researchers of the Center indicates different mechanisms for the development of asthma and allergies.

August

5. Modeling molecular networks mathematically: The bioinformatician Prof. Dr. Fabian Theis is the fourth scientist at the Center to receive a Starting Grant from the European Research Council in 2010.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16. Politicians visit summit laboratory: On top of the Zugspitze mountain, the Federal Minister of Education and Research, Prof. Dr. Annette Schavan, and CSU Secretary-General Alexander Dobrindt gather information on the Center's neutron measuring station. — 14

26. Extreme climbers as lung ambassadors: The mountaineers Alexander and Thomas Huber support the AtemWeg foundation in its efforts for more research into lung diseases. — 15


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September

29. The Center turns 50: At the Helmholtz Wiesn, 1200 employees and their families celebrate 50 years of research at Neuherberg. — 16

29. Internal award for new insights into diabetes research: The Association of Friends and Supporters awards the Paula and Richard von Hertwig Award, endowed with prize money of 5000 euros, for researching gene variants and metabolic products in complex diseases. — 17

30. Improved emergency care for the north: District Administrator Johanna Rumschöttel inaugurates the new facility for emergency physicians covering the northern administrative district of Munich. — 18


20


21


23

1. Strategic partnership for research into lung diseases: The Roche company promotes a research group at the Comprehensive Pneumology Center, which investigates options in cell therapy for chronic lung diseases.

1. EUCOMMTOOLS – providing a better understanding of diseases: The world's largest research project to elucidate the function of genes in mice is launched under the aegis of Helmholtz Zentrum München.

11. Important partner in setting up the German Centres for Health Research: Dr. Jan Grapentin, Head of Division "Life Science Research Institutions" at the Federal Ministry of Education and Research, praises the Center's strategic focus. — 19

26. Kick-off: As part of the third Doctoral Students Day, representatives of the Center and of both Munich universities officially open up the Helmholtz Graduate School "Environmental Health" (HELENA) — 21

26. Awards for excellent doctoral theses: Three female doctoral students receive the award of the Association of Friends and Supporters.

1. New head of research unit: Prof. Dr. Jörg Peter Schnitzler is the new Head of the Research Unit Environmental Engineering at the Institute of Biochemical Plant Pathology.

October

11. Exchange program established: Trainees of the German Cancer Research Center Heidelberg (DKFZ) spend 14 days training in the laboratories of Helmholtz Zentrum München. — 20

20. Isotopes for clean ground water: Leading European isotope scientists discuss current and future applications of isotopes in groundwater protection at the Center.

29. Research into lung clearance acknowledged: Dr. Wolfgang G. Kreyling receives the Thomas T. Mercer Award of the American Association of Aerosol Research and of the International Society for Aerosols in Medicine — 22

22

November

8. Involved in three further German Centres for Health Research: In addition to the German Centre for Diabetes Research and the Centre for Neurodegenerative Diseases, Helmholtz Zentrum München will also become a partner of the new German Centre for Lung Research (DZLF) as well as the new Centres for Infection Research and for Cardiovascular Research.


19


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24


26

9. Pooled expertise of five partners for the future of diabetes research: Parliamentary State Secretary Dr. Helge Braun opens the German Centre for Diabetes Research in Berlin; the Centre's office is at Helmholtz Zentrum München. — 23

11. Making communication at the Center more effective: The new series of events for executives in science and administration starts by introducing and discussing the goals for 2011.

19. Vocational training completed with distinction: Trainee animal keeper Michelle Wettstein was among the best of her year.

19. Clinical research award for medical professionals at the Center: Prof. Dr. Rolf Issels receives the AIO Science Award. — 24

7. Population surveys for health: Launching its second Institute of Epidemiology, the Center celebrates 25 years of the Cooperative Health Research Platform in the Augsburg Region (KORA) and the 20th anniversary of the Institute of Epidemiology. — 26

13. Adoro for AtemWeg foundation: In their capacity as lung ambassadors, the five singers of the opera boy band support research into and prevention of lung diseases. — 27

November

16. Recruiting junior researchers: Scholarship students of the Hans Böckler Foundation, studying medicine and biology, gather information at the Center about career options and doctoral programs.


25

23. Regulation mechanism decoded: Dr. Jovica Ninkovic receives the LMU / Scopus Neuroscience Award.

23. Department of Radiation Sciences founded: The Institutes of Radiation Protection and Radiation Biology and the independent Research Units Radiation Cytogenetics and Medical Radiation Physics and Diagnostics join forces to advance medical procedures. — 25


27

December

14. Research infrastructure developed further: Management and project managers hand over the building works completed in 2010 as part of the campus extensions to the scientists that will use them. — 28

27. New options for tumor therapy: Researchers at the Center and at Technische Universität München develop a first-ever tumor-specific antibody.


28

Vision, Research Strategy and Research Programs

Vision and Transformation

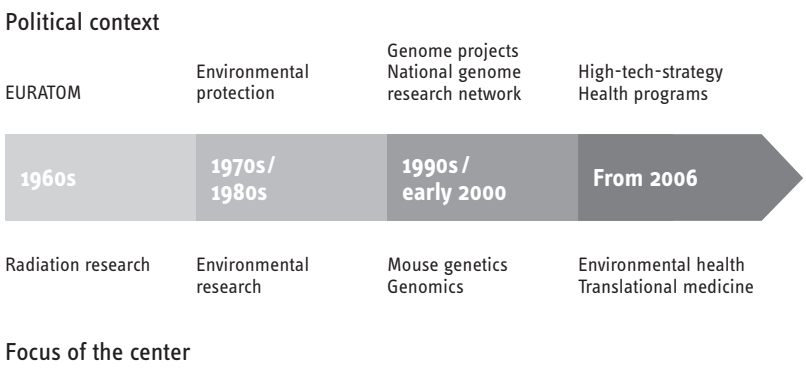
Helmholtz Zentrum München has made it its goal to improve human health. To this end we conduct research into new ways of diagnosis, therapy and prevention of common diseases, with a particular focus on diabetes mellitus and lung disease.

Transforming Health Research: Changes in Health Research at Helmholtz Zentrum München in a Social Context

During the 50 years of its existence, the focus of Helmholtz Zentrum München developed from radiation research via environmental research to health research. This transformation reflects the changed perception and social emphasis of these issues. It takes place between the conflicting priorities of social needs, political stipulations and enhanced scientific possibilities. With its research our Center makes significant contributions to solving social problems.

In 1960 the Center is founded with the goal of researching the effects of ionizing radiation on health and the environment, as well as its applicability in medicine and technology. In the late 1970s this leads to the development of systematic research into the effects of environmental factors on health and to the development of capacity in medical therapy and technology. Among the results are concepts for the early detection of environmental health risks, which provide important incentives for politicians. The Center's interdisciplinary focus, new means and method of molecular biology and genetics are the approach of the 1990s in order to build bridges between environmentally-related health risks and new medicine. At the same time it becomes more and more evident that common diseases are becoming one of society's major challenges. With its focus on environmentally-related lifestyle diseases, Helmholtz Zentrum München redefines environmental health research and sets programmatic foci on economically relevant disease patterns.

Scientific Focus of the Center in the Context of the Prevailing Research Policy



The Center's scientific focus reflects changes in the framework conditions of society and research policy. The foci shift from radiation and environmental research via genome research to the core issue of environmental health and translational medicine.

Transforming Health Research: Research and Vision

The ability to solve social issues requires both an awareness of past developments and a clear direction, a vision. As a guideline, it serves as the basis for progress and innovation. Based on new insights, science continues to challenge previous assumptions. This combination of vision and continuous challenging helps to overcome limits and break new ground – the vision serves as a signpost for transformation. Helmholtz Zentrum München has made it its goal to protect and improve human health by developing innovative diagnostics, therapies and prevention methods. To this end the Center has formulated its goal in the initiative one^{2013} – to become a worldwide leading research center in health research, focused on the field of environmental health. The basis for this goal is an above-average effort to translate science into benefits for society.

Our competencies allow us to take a unique research approach to environmental health while at the same time focusing on people: Using the combination of health research and environmental research, we uncover hitherto unknown connections between genetics, lifestyle and the environment, thus developing new approaches to diagnosis, therapy and prevention of common diseases and making a significant contribution to improved human health. We focus on diabetes mellitus and lung diseases, while at the same time using mechanistic studies for important contributions to other common diseases such as infection diseases, cardiovascular diseases or neuropsychiatric diseases.

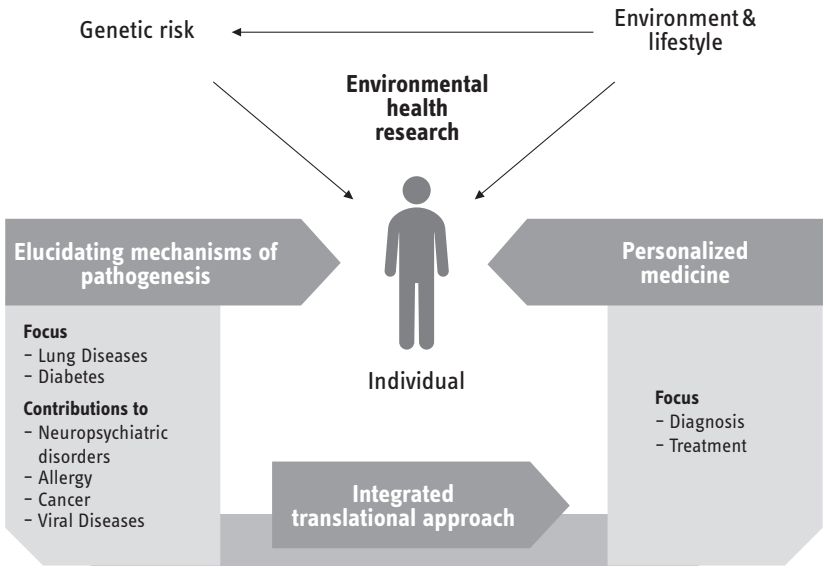
Strategic Focus on Environmental Health

Health, environment and their correlation with the most common diseases (environmental health) is the leitmotif of Helmholtz Zentrum München, the connecting element of research. The connection of mechanistic research with environmental factors leads to trend-setting results that contribute to research into common diseases, beyond lung diseases and diabetes mellitus.

Environmentally related diseases are among the great medical and socio-economic challenges of the Western world. An increasing life expectancy of the population and global environmental changes will lead to a dramatic increase in diseases such as diabetes, respiratory and cardiovascular diseases, cancer, and allergies that arise from the complex interaction of environmental factors, lifestyle and individual genetic disposition.

In recent years Helmholtz Zentrum München has made a clear commitment to its focus on environmental health: it researches how health, genetics and environmental factors, including lifestyle, interact in order to contribute to the pathogenesis of the most common diseases. The dramatic increase of chronic diseases across the world can only be explained by a concurrence of environmental factors and individual genetic predisposition. Two aspects make the research at Helmholtz Zentrum München special: on the one hand we don't just look at environmental noxa, but also include genetic aspects in order to obtain a comprehensive image of the mechanisms that make the difference between health and disease, while at the same time taking into account the individual specifics. On the other hand environmental influences are defined in much broader terms and age-specific, socio-economic and geographic factors are taken into account. One such example is a person's specific metabolic status, which is taken into account through the combination of genetic and metabolomic data. Through this approach, Helmholtz Zentrum München contributes to the development of personalized medical approaches and thus to the creation of social benefits from research.

With this goal in mind, Helmholtz Zentrum München focuses on complex chronic diseases of the lung and on diabetes mellitus. Furthermore, it uses the mechanistic research at the Center to contribute to other common diseases such as infectious diseases, cardiovascular diseases and neuropsychiatric diseases.



Research approach of Helmholtz Zentrum München: The Center's leitmotif is Environmental Health – conducting research into genetics, environment and lifestyle and their influence on the most common diseases. Armed with the knowledge of how the environment and genomes interact, the Center researches mechanisms of pathogenesis and translates this knowledge systematically into practical application.

This research approach and the skills at the Center are pooled in three strategic programs, which ensure the Center's basic funding in the context of program-oriented funding (POF) by the Helmholtz Association. The second phase of the POF runs from 2009 to 2013.

In the Environmental Health (EH) program, the main research focus is on lung diseases and on reactions of the immune system to environmentally related diseases such as allergies, specific types of tumors as well as risk factors for important common diseases. In the Systemic Analysis of Multifactorial Diseases (SAM) program, diabetes and neurological diseases are at the center of interest. There are overlapping projects in the fields of allergy, immunity, and aerosol research with interfaces between the Terrestrial Environment – Strategies for a Sustainable Response to Climate and Global Change (TE) program and the health sector. In addition, the EH and SAM programs cooperate in order to research infectious diseases and immunology as well as cardiovascular diseases.

"We are researching the correlation between environmental factors and genetic disposition in the pathogenesis of chronic diseases such as lung diseases. Based on our research, we are developing individualized strategies for prevention, early diagnosis and therapy."

Prof. Dr. Martin Göttlicher — Program Spokesperson Environmental Health

Environmental Health Program (EH)

The Environmental Health program contributes to a better understanding of the correlation between environmental factors and health and develops new, effective strategies for the prevention, early detection and treatment of chronic diseases.

Special Emphases in the Environmental Health Program

Lung diseases: Helmholtz Zentrum München is conducting research to develop new therapies for chronic lung diseases. It is committed to providing faster utilization of research results for the benefit of patients through a translational research approach. Helmholtz Zentrum München founded the Comprehensive Pneumology Center (CPC), a translational research center for lung research, in cooperation with Ludwig-Maximilians-Universität Munich and the Asklepios Pulmonary Hospital Gauting. The CPC is located on the high-tech campus in Großhadern and is embedded in modern research and clinical infrastructures. Its scientific research laboratories and research clinic cooperate with the Asklepios Pulmonary Hospital in München-Gauting and the university hospital of Ludwig-Maximilians-Universität.

Disease risks: Together with the German Cancer Research Center (DKFZ), Helmholtz Zentrum München has assumed the leading role in planning a major national cohort for analyzing disease risks in the population. This nation-wide cohort, which will be in place for up to twenty years, will examine risk factors in 200 000 individuals for common diseases such as diabetes, cancer, neurological diseases and cardiovascular diseases and will open up new avenues for their prevention.

Environmental Health Program

Coordination
Helmholtz Zentrum München

Program Spokesperson
Prof. Dr. Martin Göttlicher

Participating Centers (share in %)
Helmholtz Zentrum München (90 %)
Helmholtz Centre for Environmental Research Leipzig (10 %)

"The next great challenge will be to find out how genetic factors contribute to the development of multifactorial diseases and under which pre-conditions and environmental conditions systemic diseases arise. Our aim is to analyze the essential genetic factors and biomolecular principles that lead to multifactorial diseases – for example in diabetes mellitus."

Prof. Dr. Martin Hrabě de Angelis — Program Spokesperson Systemic Analysis of Multifactorial Diseases

Systemic Analysis of Multifactorial Diseases (SAM) Program

Multifactorial diseases have a major impact on the disease and mortality rate of a society. They arise from the complex interaction of an individual genotype with environmental and lifestyle factors. The Systemic Analysis of Multifactorial Diseases program (SAM) combines functional genomics in model systems, i.e. studies in cell systems and animal models, with human genetics. Through research approaches of systems biology, it searches for "functional modules", i.e. biological functional units that cause disease when disrupted. The German Mouse Clinic, an open access platform that serves as an instrument for the standardized analysis of mouse models for human diseases, is run under the aegis of the SAM program.

Special Emphases in the Systemic Analysis of Multifactorial Diseases Program

Diabetes mellitus: Helmholtz Zentrum München has joined forces with Ludwig-Maximilians-Universität and Technische Universität München to form a strategic partnership in diabetes research. In 2010 the German Centre for Diabetes Research e. V. (DZD) was founded, which pools national competence with the aim of rapidly providing benefits to diabetic patients. The DZD office is located at Helmholtz Zentrum München.

Neurological and psychiatric disorders: At Helmholtz Zentrum München two institutes conduct research on the brain and the nervous system, neurodegeneration and neuroregeneration. The Center also coordinates the Helmholtz Alliance "Mental Health in an Ageing Society." Helmholtz Zentrum München is also involved in the Munich partner location of the German Centre for Neurodegenerative Diseases (DZNE) in Bonn.

Systemic Analysis of Multifactorial Diseases Program

Coordination
Helmholtz Zentrum München

Program Spokesperson
Prof. Dr. Martin Hrabě de Angelis

Participating Center
Helmholtz Zentrum München

"The idea of ecosystem services is a key aspect of the Terrestrial Environment program. The question of how the components soil, water and plants can be utilized for human benefits is of prime importance."

Prof. Dr. Jörg Durner — Program Spokesperson Terrestrial Environment at Helmholtz Zentrum München

Terrestrial Environment Program (TE)

Terrestrial systems are the place where human activities propel global change. At the same time they are the habitat in which humans are directly affected in their living and economic conditions. The aim of research in the Helmholtz program "Terrestrial Environment" is to secure the natural foundations for life and health, while at the same time creating opportunities for social and economic developments. The goals of Helmholtz Zentrum München are in particular:

- to make effective contributions to the optimized utilization of microorganisms and plants
- to define and optimize ecosystem services such as food and drinking water
- to gain insights into the prevention of environmentally related diseases such as allergies or infection diseases
- to gain a better understanding of biological mechanisms and guide processes, ranging from molecules to organisms and environmental habitats; and
- to explain sensitivity towards various influential factors.

Special Emphasis in the Terrestrial Environment Program:
Helmholtz Zentrum München researches emphatically how water quality can be measured and preserved. In cooperation with Technische Universtität München, the University of Bayreuth and the Water Resources Authority in Hof, Bavaria, Helmholtz Zentrum München is in the process of establishing a Bavarian Center for Water Research. Another focus is the research of defense mechanisms in plants as well as efficient use of resources. Together with the plant biology laboratories at both Munich universities, particular priority is given to the research of molecular mechanisms which allow plants to react to biotic and abiotic factors.

Terrestrial Environment Program – Strategies for a Sustainable Response to Climate and Global Change (TE)

Coordination
Helmholtz Centre for Environmental Research Leipzig

Program Spokesperson
Prof. Dr. Bernd Hansjürgens, Leipzig

Program Spokesperson within Helmholtz Zentrum München
Prof. Dr. Jörg Durner, München

Participating Centers (share in %)
Helmholtz Centre for Environmental Research Leipzig (55 %)
Research Centre Jülich (23 %)
Helmholtz Zentrum München (22 %)

Activities across Programs

Infectious Diseases and Immunology: Research into infectious diseases forms an interface between the Center's three programs – EH, SAM, and TE. In addition to the different scientific approaches for the elucidation of molecular and genetic pathomechanisms in EH and SAM, TE supports the search for innovative therapies for infectious diseases.

Helmholtz Zentrum München researches chronic infectious diseases such as hepatitis and related liver diseases, as well as human endogenous retroviruses and the consequences of these diseases. It develops diagnostic and therapeutic concepts as well as strategies in order to prevent viral diseases or the development of tumors. Together with Technische Universität München, Ludwig-Maximilians-Universtität and the Institute of Microbiology of the Bundeswehr, the Center is involved in the Munich partner location of the German Centre for Infection Research envisaged for 2011.

Common Focus of the EH and SAM Programs

Cardiovascular Diseases: With its expertise from large population surveys, Helmholtz Zentrum München contributes to the etiology of cardiovascular diseases. Priority is given to the analysis of genetic factors and their interaction with environmental influences and lifestyle. As part of the Munich Heart Alliance established in 2010, Helmholtz Zentrum München is involved in the German Centre for Cardiovascular Research, which is due to take up its work in 2011. The Munich Heart Alliances pools the competencies of both Munich universities, the Max Planck Institute of Biochemistry, and Helmholtz Zentrum München in order to boost in particular the translation of insights from basic research into clinical research and application.

The EH and SAM programs cooperate closely for researching cardiovascular diseases. They contribute their different scientific approaches in order to gain a better understanding of molecular and genetic mechanisms of the cause of diseases and to develop new strategies for their prevention and treatment.

Common Focus of the EH and TE Programs

Allergies: Together with Technische Universität München, Helmholtz Zentrum München has established a new Allergy Center with the aim of understanding the causes of allergies and to develop therapeutic approaches for their treatment. Using its expertise, the TE program contributes to researching allergies in the field of plants and pollen.

Translational Research

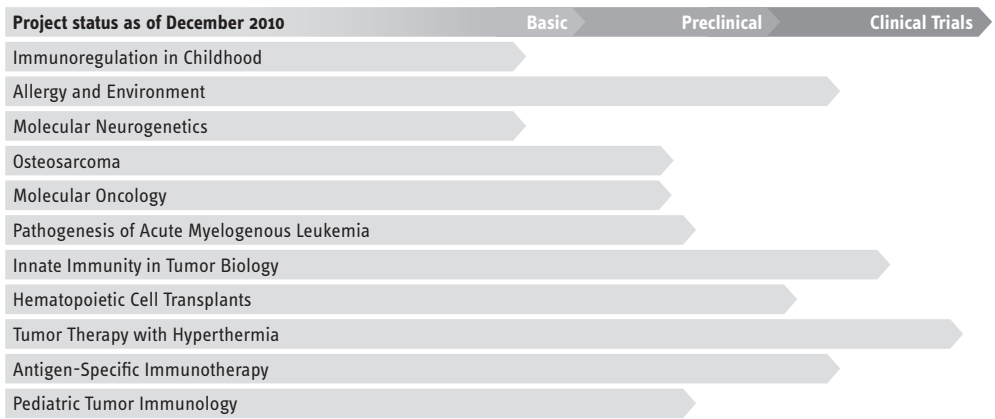
Translational research is an integral part of our approach to research at Helmholtz Zentrum München. It allows us to further develop knowledge into medical progress and to harness the potential of knowledge gained through basic research for medical practice. The goal of our close cooperation with the university hospitals in Munich is to quickly provide patients with new and improved therapy and diagnostic procedures.

There are still no treatment approaches for the most common diseases, which can fight their causes or even prevent them. As the German Research Center for Environmental Health, Helmholtz Zentrum München has made it its business to improve this situation and to develop individualized options for diagnosis and therapy.

Translational research in medicine aims to provide effective, safe, and affordable answers to pressing matters of health care for patients and the society at large. In clinical cooperation groups and the translational center for lung research (Comprehensive Pneumology Center – CPC), scientists and clinicians cooperate closely in order to better understand chronic complex diseases, thus allowing them to treat these more effectively in the future. Based on the latest knowledge, clinical observations and findings, as well as up-to-date technology, scientific hypotheses are developed that are then examined at the hospital for their correctness and usability. The influence of genetic predisposition and environmental factors on the individual disease risk, the pathogenesis and the progress of the disease are then considered all together. In the future, this integrated research approach will lay the foundations for providing evidence-based personalized prevention and therapy concepts. In this context, clinical cooperation groups are the focal point of personalized medicine.

In order to strengthen this focal point as best as possible, Helmholtz Zentrum München is focusing its organizational structure on successful translational research by creating clear links to hospital. Scientists dedicated to translational research in clinical cooperation groups combine clinical and scientific expertise. This leads to the creation of new teams with a clinical, market-oriented and science-oriented focus; their highest priority is human health.

Status of Clinical Projects



Overview: Translational Research Center for Lung Research and Clinical Cooperation Groups 2010

Lung

Comprehensive Pneumology Center
Head: Prof. Dr. Oliver Eickelberg
Partner: Helmholtz Zentrum München | Institute of Lung Biology, Ludwig-Maximilians-Universität Munich, Asklepios Pulmonary Hospital München-Gauting

Immunoregulation in Childhood
Head: PD Dr. Susanne Krauss-Etschmann
Partner: Helmholtz Zentrum München | Institute of Lung Biology, Ludwig-Maximilians-Universität Munich

Allergy

Allergy and Environment
Head: Prof. Dr. Carsten Schmidt-Weber
Partner: Helmholtz Zentrum München | Institute of Lung Biology, Technische Universität München

Pathomechanisms and Therapeutical Targets

Molecular Neurogenetics
Head: Prof. Dr. Wolfgang Wurst
Partner: Helmholtz Zentrum München | Institute of Developmental Genetics, Max-Planck-Institute of Psychiatry

Molecular Oncology
Head: Prof. Dr. Olivier Gires
Partner: Helmholtz Zentrum München | Resarch Unit Gene Vectors, Ludwig-Maximilians-Universität Munich

Osteosarcoma
Head: PD Dr. Michaela Nathrath
Partner: Helmholtz Zentrum München | Institute of Pathology, Technische Universität München

Pathogenesis of Acute Myelogenous Leukemia
Head: Prof. Dr. Wolfgang Hiddemann
Partner: Helmholtz Zentrum München | Institute of Clinical Molecular Biology and Tumor Genetics Ludwig-Maximilians-Universität Munich

Innovative Therapies

Innate Immunity in Tumor Biology
Head: Prof. Dr. Gabriele Multhoff
Partner: Helmholtz Zentrum München | Institute of Pathology, Technische Universität München

Immune Monitoring (Platform)
Head: Prof. Dr. Dolores Schendel
Partner: Helmholtz Zentrum München | Institute of Molecular Immunology, Ludwig-Maximilians-Universität and Technische Universität München

Hematopoietic Cell Transplants
Head: Prof. Dr. Wolfgang Hiddemann (acting)
Partner: Helmholtz Zentrum München | Institute of Molecular Immunology, Ludwig-Maximilians-Universität Munich

Pediatric Tumor Immunology
Head: Prof. Dr. Uta Behrends
Partner: Helmholtz Zentrum München | Research Unit Gene Vectors, Technische Universität München

Tumor Therapy with Hyperthermia
Head: Prof. Dr. Rolf Issels
Partner: Helmholtz Zentrum München | Institute of Molecular Immunology, Ludwig-Maximilians-Universität Munich

Antigen-Specific Immunotherapy
Head: Prof. Dr. Dirk Busch
Partner: Helmholtz Zentrum München | Institute of Virology, Technische Universität München

Technology Transfer

The foremost goal of technology transfer is to make the results of our research work available for concrete application as soon as possible, in cooperation or with the help of our industrial partners. Technology transfer is a key function of the business model of Helmholtz Zentrum München.

Helmholtz Zentrum München has a broad range of new and competitive technologies, especially in the fields of biotechnology, pharmaceutics and medical technology as well as environmental analytics. Ascenion GmbH, which was founded on the initiative of Helmholtz Zentrum München, and our Legal and Technology Transfer Department make these technologies available for utilization by the industry. In this process Ascenion GmbH supports the research center in the commercialization of technologies and patents developed at the Center.

Patenting and out-licensing as well as spin-offs constitute an important basis of technology transfer at Helmholtz Zentrum München. In 2010 the Center's patent portfolio comprised 131 patent families. Nearly 20 inventions resulted in 15 invention disclosures, of which 10 inventions were submitted as patent applications after evaluation by Ascenion GmbH.

Business Start-ups by Helmholtz Zentrum München

In 2010 two start-up companies were founded. eADMET GmbH is a chemoinformatics IT company specializing in physicochemical and ADMET property predictions. ADMET stands for "Absorption, Distribution, Metabolism, Excretion, and Toxicity". The company develops and distributes web-based solutions for data storage, integration, interpretation and model creation of pharmacological agents. iThera Medical GmbH was also founded in 2010 and offers innovative technologies and know-how based on multi-spectral optoacoutstic tomography (MSOT) for use in preclinical and clinical applications; this technology was developed in cooperation with Helmholtz Zentrum München. The company's business is based on four patent applications by Helmholtz Zentrum München, aimed at securing the technology. In 2010 iThera Medical received a GO-BIO award and the BioVaria spin-off award. In recent years twelve companies with currently around 340 employees have emerged from the Center.

Spin-offs

ACTIVAERO GmbH
Founded 1998 as Inamed GmbH – since 2006 device development under the name of Activaero GmbH – a competence center for inhalation technology and aerosol medicine
www.activaero.de

Biomax Informatics AG
Founded in 1997 – develops bioinformatics software for the life science industry
www.biomax.com

eADMET GmbH
Founded in 2010 – physicochemical and metabolic predictions of pharmacological agents
www.eadmet.com

Genomatix Software GmbH
Founded in 1997 – programs for elucidating mechanisms and reaction processes in biological systems
www.genomatix.de

Inamed Research GmbH & Co. KG
Founded in 1998 – investigation of systems and procedures for drug inhalation
www.inamed.de

Ingenium Pharmaceuticals GmbH
Founded in 1997 – integration into Probiodrug AG in 2007 – development of small molecules for the treatment of neuronal and autoimmune diseases
www.probiodrug.de

iThera Medical GmbH
Founded in 2010 – non-invasive imaging procedures based on molecular laser technology
www.ithera-medical.com

Isodetect GmbH
Founded in 2005 – isotopic monitoring of environmental bioremediation
www.isodetect.de

MedTherm GmbH
Founded in 2008 – hyperthermia as a treatment for cancer

Photonion GmbH
Founded in 2009 – development of mass spectrometric devices for the direct analysis of complex organic substances
www.ascenion.de

Sirenade Pharmaceuticals AG
Founded in 2005 – taken over by KeyNeurotek AG – focus on neurodegenerative diseases
www.keyneurotek.de

TRION Pharma GmbH
Founded in 1998 – cancer immunotherapy based on trifunctional antibodies
www.trionpharma.de

Vaecgene GmbH
Drugs for the treatment of tumors and infectious diseases
www.vaecgene.de

Vivacs GmbH
Taken over in 2005 by Biosolutions – vaccine vector technologies
www.emergentbiosolutions.com

Transformation for the Benefit of Society AKITA – a Success Story

With the inhalation system AKITA, up to 85 percent of the active agent used can be deposited in the lung – thereby setting new standards. AKITA was developed at Helmholtz Zentrum München, out-licensed and made ready for the market. The development of AKITA proves the innovative potential of Helmholtz Zentrum München.

For its development of the AKITA Jet inhalation system, the company Activaero GmbH – a spin-off of Helmholtz Zentrum München – received the special award "New Products and Development" in the competition "Hessen Champions 2010".

This special device for the treatment of serious lung diseases makes it possible to deposit a very large amount of the often very expensive active drug in the lung. Using this inhalation system, up to 85 percent of the active agent used can be deposited in the lung – compared to an average rate of 15 percent.

New gold standard – 85 percent active agent in the lung

The AKITA inhalation system is the result of research at the Institute of Inhalation Biology at Helmholtz Zentrum München. Researchers there looked at biophysical parameters of the distribution of small particles in the lung. A group of scientists, led by Dr. Gerhard Scheuch, applied this knowledge to the improvement of treatment success in drug inhalation. They developed an automatic inhalation system which patients can use for the controlled inhalation of drugs particles.

In 1998 Gerhard Scheuch founded the company Inamed GmbH, located in Gauting near Munich and in Gemünden, Hesse. In 2002 Inamed marketed the prototype of the AKITA inhalation system: Using a smart card, it is adjusted precisely to a specific drugs therapy. In addition to patient data, this smart card also stores the ideal inhalation pattern, calculated individually for each patient. The device only allows the optimum breathing maneuver. This ensures that a significantly improved therapeutic effect is achieved.

In 2004 the company split up the business divisions Contract Research and Device Development. For device development, a new company with the name Activaero GmbH was established, which has, since then, become the world leader in the development of controlled breathing drug delivery technologies.

A cooperation project between Activaero GmbH and the Institute of Lung Biology at Helmholtz Zentrum München resulted in an inhalation aid suitable for children, which mechanically controls the inhalation flow and the inhaled volume for the administration of asthma drugs. This is aimed at increasing the acceptance of the therapy, while at the same time optimizing the drug inhalation. In 2007 the first inhalation device for children was marketed, bearing the name WATCHHALER. This project was supported by the German Federation of Industrial Research Associations (AiF) with funding from the Federal Ministry of Economics and Technology.

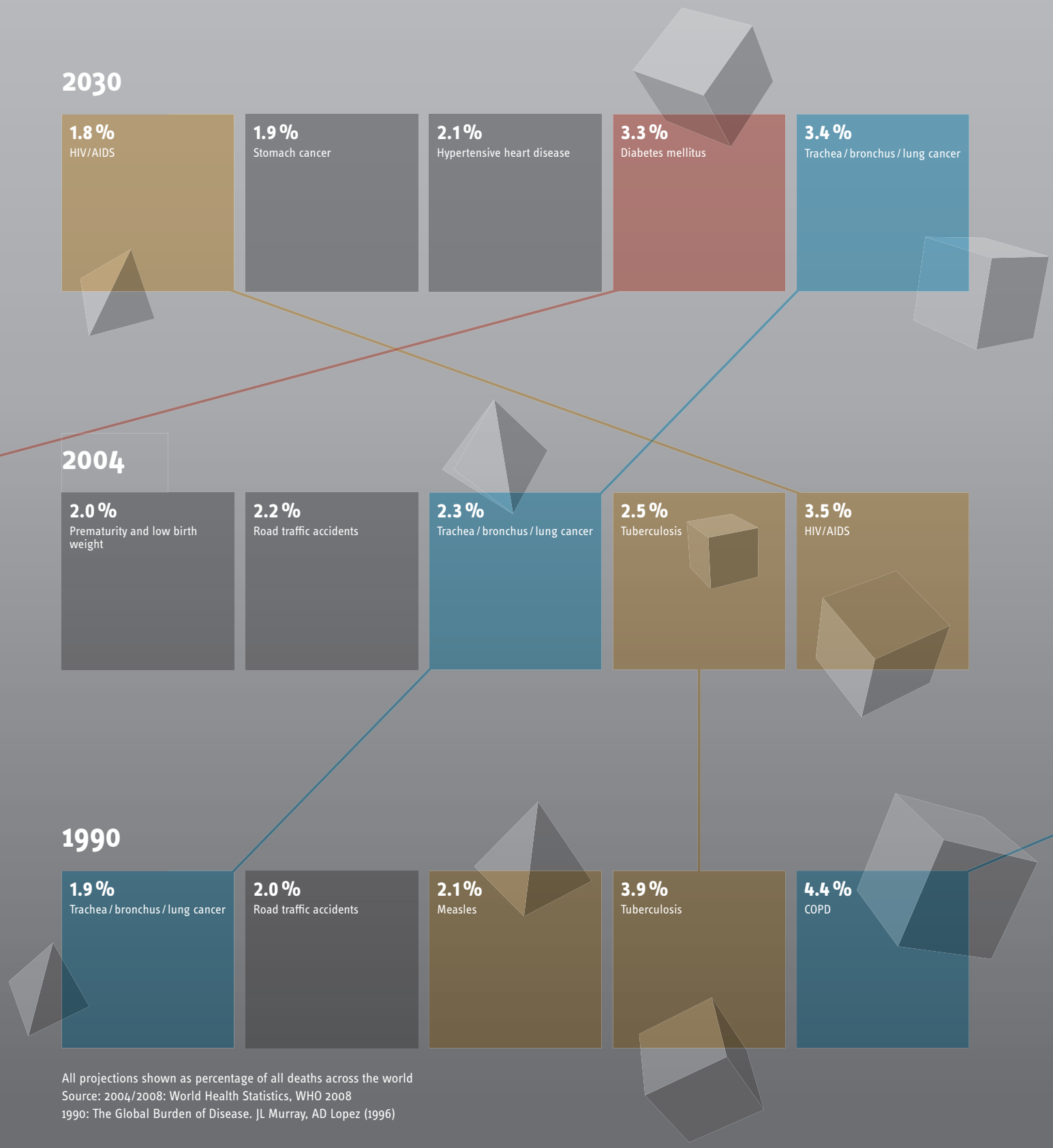
The development of the AKITA Jet inhalation system, which won an award in 2010, had been supported by the Hessian Initiative for the Development of Scientific and Economic Excellence (LOEWE). In the period 2009 / 2010, Activaero raised a total of 15.6 million euros in a round of funding.

Activaero – 42 employees, worldwide technology leader for controlled inhalation

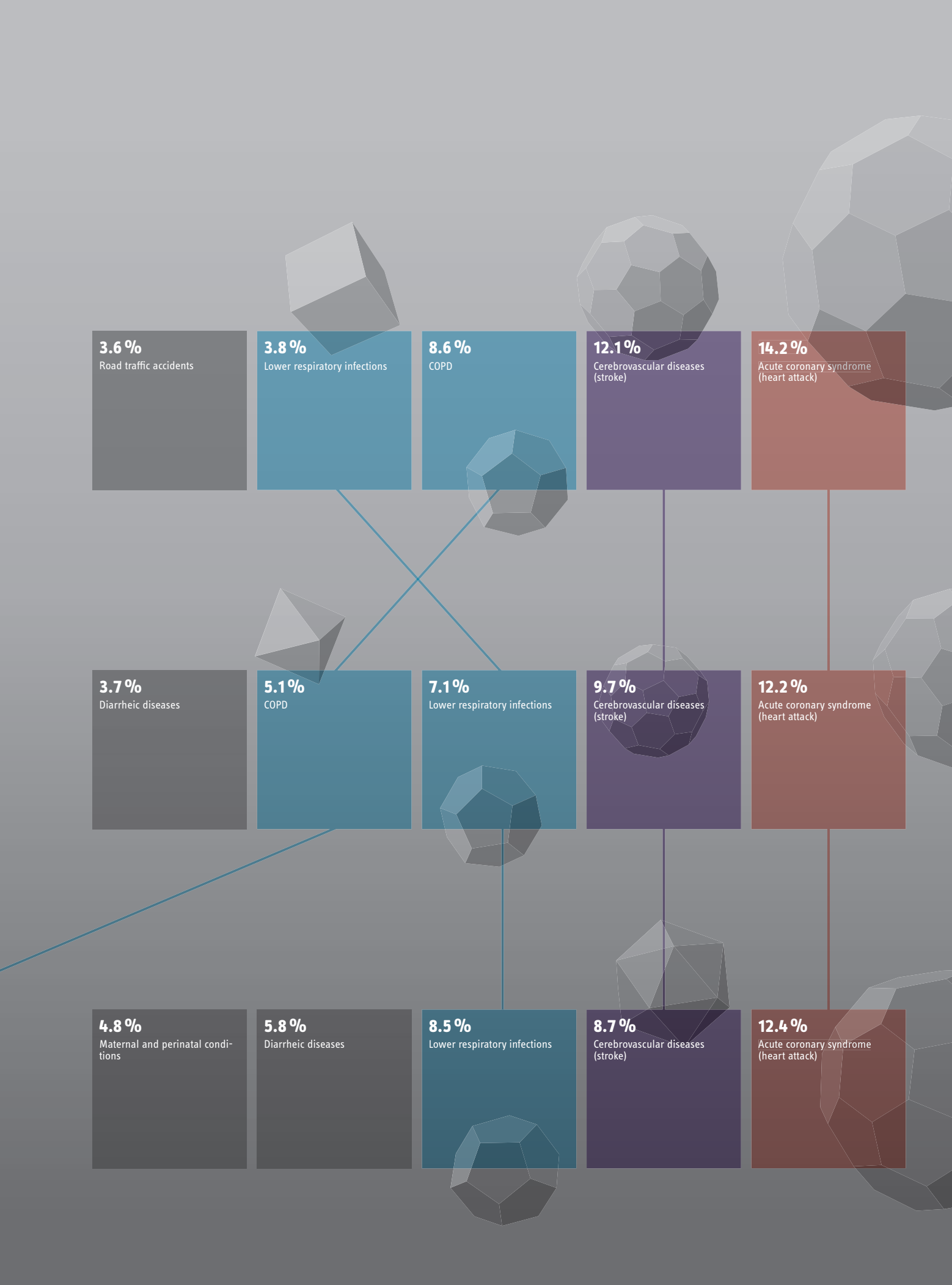
After approval of the first therapeutic antibody developed in Germany by Trion Pharma GmbH, which is based on immunological research at the Center, the success of the inhalation systems developed by Activaero GmbH confirms once again the model of technology transfer and translational research applied at Helmholtz Zentrum München. Results with high application potential are developed further and brought to clinical trials. Spin-offs and cooperation enable development to market maturity. In doing so the Center receives a share of the value creation and royalties from the research results. The revenue thus generated is then reinvested in supporting new, innovative research or development projects at the Center.

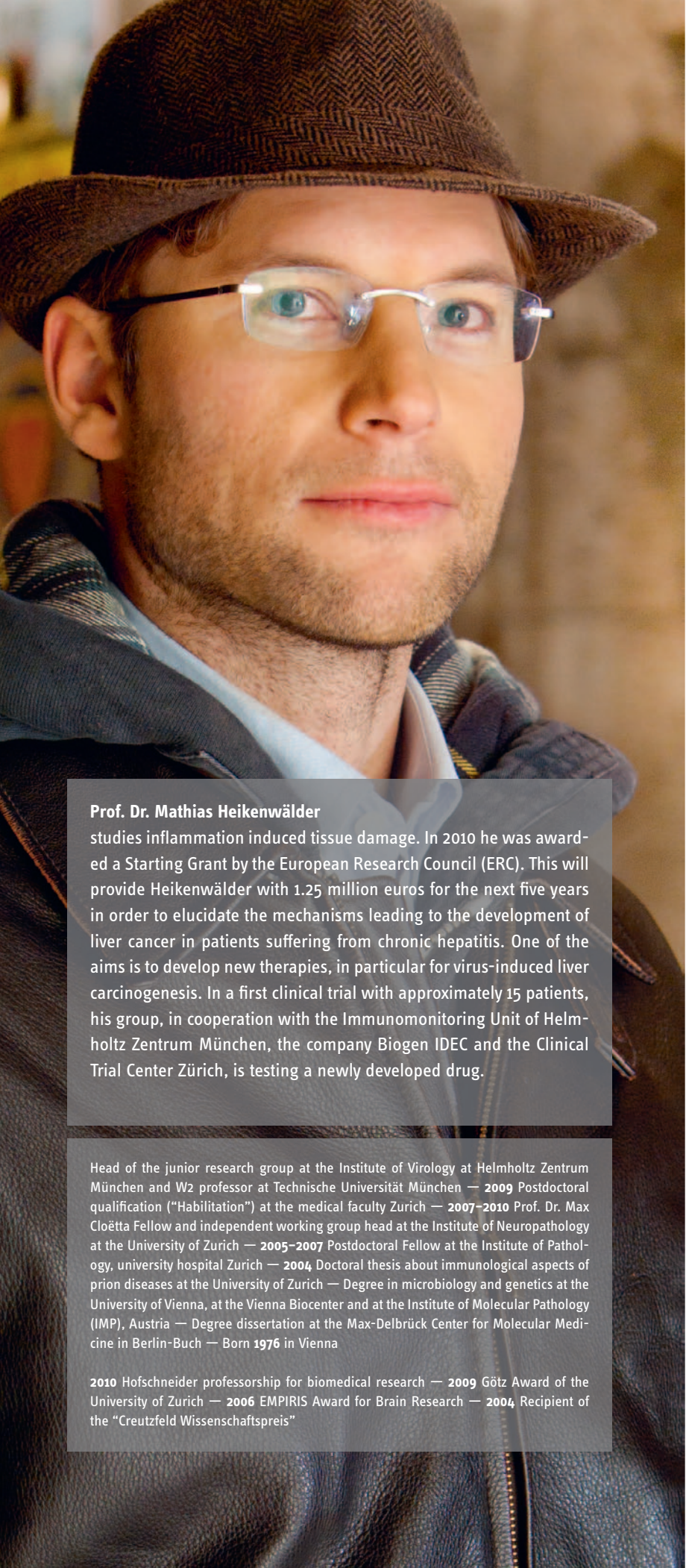
Diseases through the Ages

The most frequent causes of death 1990 – 2030



All projections shown as percentage of all deaths across the world
Source: 2004/2008: World Health Statistics, WHO 2008
1990: The Global Burden of Disease. JL Murray, AD Lopez (1996)


3.6 %
Road traffic accidents
3.8 %
Lower respiratory infections
8.6 %
COPD
12.1 %
Cerebrovascular diseases (stroke)
14.2 %
Acute coronary syndrome (heart attack)
3.7 %
Diarrheic diseases
5.1 %
COPD
7.1 %
Lower respiratory infections
9.7 %
Cerebrovascular diseases (stroke)
12.2 %
Acute coronary syndrome (heart attack)
4.8 %
Maternal and perinatal conditions
5.8 %
Diarrheic diseases
8.5 %
Lower respiratory infections
8.7 %
Cerebrovascular diseases (stroke)
12.4 %
Acute coronary syndrome (heart attack)



Prof. Dr. Mathias Heikenwälder
studies inflammation induced tissue damage. In 2010 he was awarded a Starting Grant by the European Research Council (ERC). This will provide Heikenwälder with 1.25 million euros for the next five years in order to elucidate the mechanisms leading to the development of liver cancer in patients suffering from chronic hepatitis. One of the aims is to develop new therapies, in particular for virus-induced liver carcinogenesis. In a first clinical trial with approximately 15 patients, his group, in cooperation with the Immunomonitoring Unit of Helmholtz Zentrum München, the company Biogen IDEC and the Clinical Trial Center Zürich, is testing a newly developed drug.

Head of the junior research group at the Institute of Virology at Helmholtz Zentrum München and W2 professor at Technische Universität München — **2009** Postdoctoral qualification ("Habilitation") at the medical faculty Zurich — **2007–2010** Prof. Dr. Max Cloëtta Fellow and independent working group head at the Institute of Neuropathology at the University of Zurich — **2005–2007** Postdoctoral Fellow at the Institute of Pathology, university hospital Zurich — **2004** Doctoral thesis about immunological aspects of prion diseases at the University of Zurich — Degree in microbiology and genetics at the University of Vienna, at the Vienna Biocenter and at the Institute of Molecular Pathology (IMP), Austria — Degree dissertation at the Max-Delbrück Center for Molecular Medicine in Berlin-Buch — Born **1976** in Vienna

2010 Hofschneider professorship for biomedical research — **2009** Götz Award of the University of Zurich — **2006** EMPIRIS Award for Brain Research — **2004** Recipient of the "Creutzfeld Wissenschaftspreis"

Moderation and Reduction of Negative Influences

Starting Grant from the European Research Council for

Mathias Heikenwälder

“Moderate intakes of alcohol and fatty food in industrialized countries and the prevention of viral infections in developing countries are a good precaution against liver cancer. Across the world it is primarily viral infections through the hepatitis B and C virus that act as a central trigger. The hepatocellular carcinoma is the third most common cause of death from cancer and claims approximately 800 000 lives across the world every year. Cell toxic cytokines play a key role in the induction of liver cancer by viruses. It is at this mechanical level that I am looking for new pharmacological approaches for the successful treatment of hepatitis and liver cancer – even for the 40 to 50 percent of patients that do not respond to the therapies currently available.”

Metabolic Research

at Helmholtz Zentrum München since 1960

1969
Foundation of the research group Medical Data Processing – Center takes up issues of prevention and health care

1984
Institute of Medical Informatics and Systems Research conducts research for improved treatment of diabetics

1989
Evaluation of expert systems for the support of therapies in the treatment of diabetes

1990
As part of EURODIABETA the Center is involved in the development of doctors' systems for the control of diabetes

1992
Development of a patient chip card for diabetics

1997
Center starts research into the consequences of diabetes mellitus with over 1000 participants

1998
Study on retina telescreening in diabetics

The Future

Breaking new ground in integrative research and clinical translation in order to successfully fight and prevent diabetes

2009
Foundation of the Institute of Diabetes Research Type 1

2009
Helmholtz Zentrum München becomes a partner of the German Centre for Diabetes Research (DZD)

2001
As part of the KORA project, the diabetes family survey starts with over 1800 participants

2008
Metabolomics Platform allows for new approaches to investigate metabolic processes

2004
Mouse model for the development of hypercholesteremia

2007
Mouse model for the loss of function in beta cells during the development of diabetes

2008
Late-onset diabetes is researched as part of the KORA Age Project

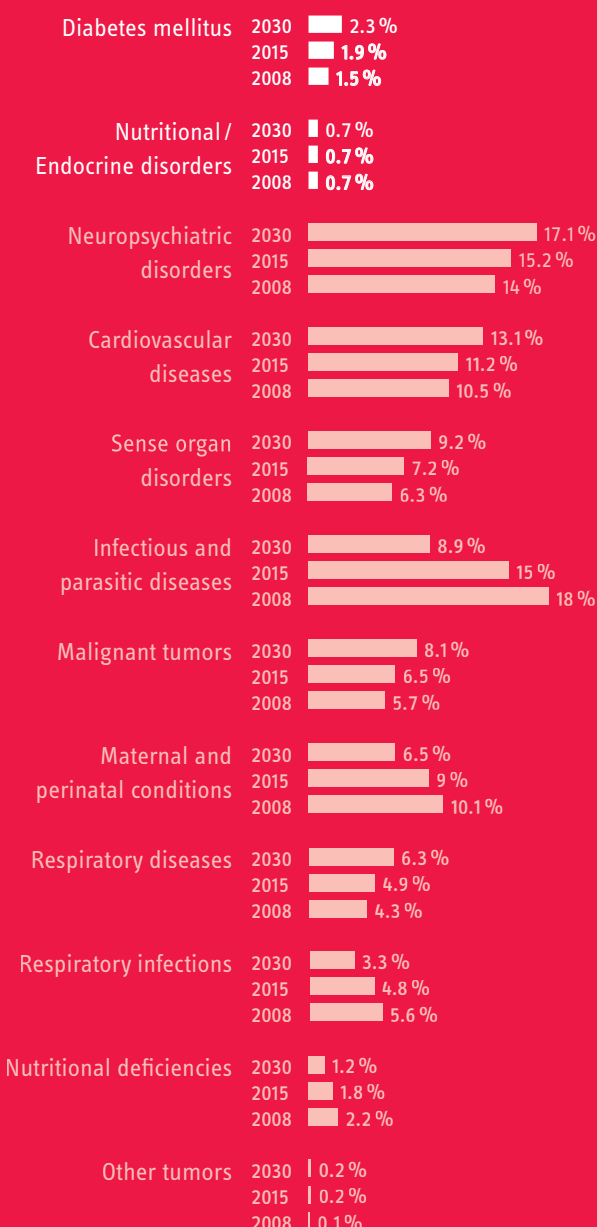
2008
The research group Insulin Resistance takes up its work

1999
The Genome Analysis Center starts its analysis of metabolically relevant gene markers

Partner of the German Centre for Diabetes Research (DZD)

Helmholtz Zentrum München

Causes of the Global burden of Disease: Diabetes Cases Increase in Epidemic Proportions



These projections show the share of the overall burden of disease in percent, stated in DALYs.

One DALY (Disability Adjusted Life Year) is a year of healthy life lost to disability. The "DALY" figure aims to not just summarize the mortality, but also the impairment of the normal life, free of complaints, through an illness, by providing a comparable measure.

Source: Projections of mortality and burden of disease, world health organisation, baseline scenarios 2008, 2015, 2030
www.who.int/healthinfo/global_burden_disease/projections/en/index.html

The **German Centre for Diabetes Research e. V. (DZD)** is one of the indication-specific national Centres for Health Research, which the Federal Ministry of Education and Research is currently establishing. It was founded in 2010. Helmholtz Zentrum München is one of five scientific partners, in addition to the German Diabetes Center (DDZ), the German Institute of Human Nutrition (DifE), the Paul-Langerhans-Institutes of the University of Tübingen, and the University Hospital Dresden. The registered office of the DZD is in Berlin. The staffed office of the DZD is at Helmholtz Zentrum München.

"As a partner of the German Centre for Diabetes Research, it is our goal to successfully fight diseases of the sugar metabolism. Diabetes mellitus is one of the common diseases and as such a focal point of Helmholtz Zentrum München. For a comprehensive understanding of this complex disease, we combine different scientific disciplines and make important contributions to developing new approaches for the prevention, diagnosis and therapy of diabetes mellitus."

Prof. Dr. Martin Hrabě de Angelis, Director of the Institute of Experimental Genetics at Helmholtz Zentrum München and Chair of Experimental Genetics at Technische Universtität München, is the coordinator of diabetes research at Helmholtz Zentrum München.

New Genetic Risk Factors for Type 2 Diabetes

"According to the current status of research, including our study results, 38 gene variants are known to play a role in the development of type 2 diabetes. From these we can develop new approaches to elucidate the underlying biological mechanisms and learn more about the risk factors – even for other chronic diseases."

An international consortium including Helmholtz Zentrum München has discovered 12 new gene variants that influence individual risk for type 2 diabetes. The study makes an important contribution to understanding the complex development of this important widespread disease.

To elucidate the genetic causes of type 2 diabetes mellitus, scientists from Germany, the United States, Great Britain, Iceland and eight other countries have analyzed the data of more than 140 000 study participants.Thomas Illig, research unit leader at the Institute of Epidemiology of Helmholtz Zentrum München, is one of the corresponding authors of the study.

Through the analyses, 12 new genetic risk factors could be identified, of which 11 have an impact on insulin production and / or action.

For the first time a genetic association was also shown between type 2 diabetes and the X chromosome. This could be a first indication of gender differences in diabetes risk: Women have two X chromosomes, men have one X and one Y chromosome. Altogether, 38 genetic risk factors for type 2 diabetes are now known.

Prof. Dr. Thomas Illig

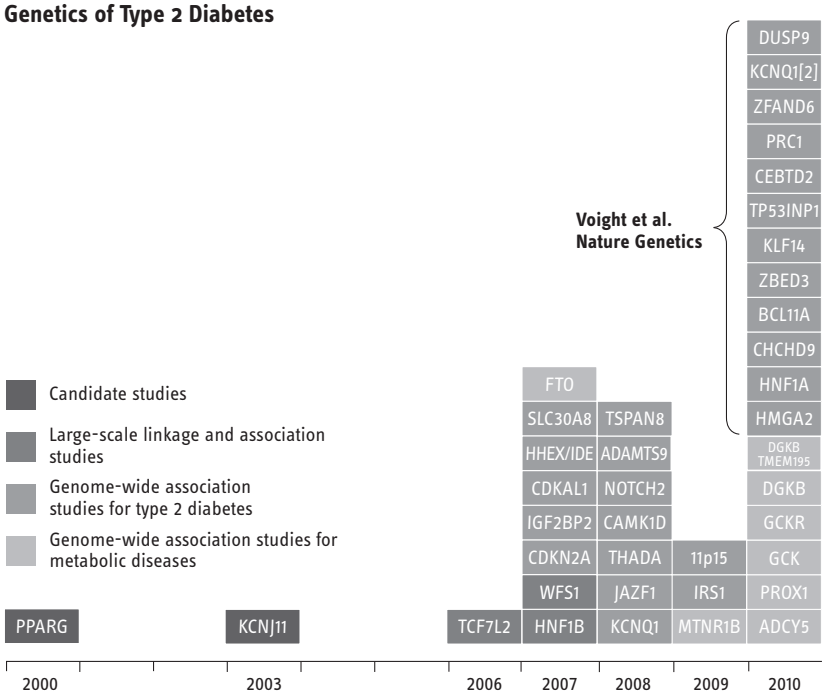
since 2011 Head of the independent Research Unit Molecular Epidemiology, Helmholtz Zentrum München, and associate professor at Ludwig-Maximilians-Universität Munich — **2010 and 2005** Paula and Richard von Hertwig Award for Interdisciplinary Cooperation at Helmholtz Zentrum München — **2006** Herbert Herxheimer Award of the German Society of Allergy and Clinical Immunology (DGAKI) — **2006** Habilitation, Ludwig-Maximilians-Universität Munich — **since 2001** Group leader of the research group Molecular Epidemiology at the Institute of Epidemiology, Helmholtz Zentrum München — **Since 1996** Research associate, Institute of Epidemiology

Cooperation Partners / Authors

158 international scientists as well as members of the MAGIC Investigators and GIANT Consortium

Helmholtz Zentrum München Cornelia Huth, Harald Grallert, Christian Gieger, Norman Klopp, Ann-Kristin Petersen, Barbara Thorand, H.-Erich Wichmann, Thomas Illig, Thomas Meitinger

Genetics of Type 2 Diabetes



So far, 38 loci for type 2 diabetes have been identified, twelve of them in this study.

Knowledge of the exact causes of type 2 diabetes is likely to result in more effective prevention strategies and therapeutic approaches to combat this widespread disease. Large numbers of study participants are required for researchers to identify such factors with high statistical accuracy; seen individually, these factors represent only a minimal contribution to the total risk. However, to elucidate the pathogenic mechanisms of the disease, even these slight contributions are of great significance.

Another important finding of the new study is that some of the loci associated with an increased risk for type 2 diabetes are also risk variants for other diseases such as coronary heart disease, autoimmune diseases or cancer. This suggests that specific proteins could be relevant for several diseases at the same time.

Type 2 diabetes is a disease of the glucose metabolism in which the effect and sufficient production of the hormone insulin become lost. The pathogenesis of the disease is not fully understood, but it is known that a combination of genetic and lifestyle factors leads to diabetes. In Germany, type 2 diabetes currently has been diagnosed in at least seven percent of the population.

Original Publication

Benjamin F. Voight et al.: Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat. Gen. 42 (2010) 579-89 | doi:10.1038/ng.

The Diabetes Marker Glycohemoglobin Is Genetically Influenced

"The analysis of the genetic basis of common chronic diseases is still in its infancy. However, in the future the results of genetic research may help make medical treatment more individualized. Then treatment choices would no longer be made solely on the basis of disease symptoms, but would also be adapted to the patient's genetic predisposition."

Dr. Christian Gieger

2010 Paula and Richard von Hertwig Award for Interdisciplinary Cooperation — **since 2009** Group leader of the research group Genetic Epidemiology — **since 2004** Research associate at Helmholtz Zentrum München and at Ludwig-Maximilians-Universität Munich — **1999–2004** Researcher in industry and at the Fraunhofer Institute St. Augustin

Cooperation Partners / Authors

179 international scientists from 103 institutions
Helmholtz Zentrum München Christian Gieger, Angela Döring, Harald Grallert, Thomas Illig, Christa Meisinger, Thomas Meitinger, H.-Erich Wichmann, Juliane Winkelmann

The concentration of glycated hemoglobin (A1C) is an important marker for type 2 diabetes mellitus. A meta-analysis shows that genetic variability can influence HbA1C levels.

The variability of the marker HbA1C can be associated with ten different regions in the human genome. This genetic variability can influence the concentration of the marker in the blood. A research group led by Christian Gieger at Helmholtz Zentrum München, together with colleagues from the UK, the USA and Italy, evaluated the results of 23 genome-wide association studies and eight additional cohort studies. In the study – the largest study of its kind in the world – the researchers based their findings on the data of nearly 50 000 nondiabetic individuals of European ancestry.

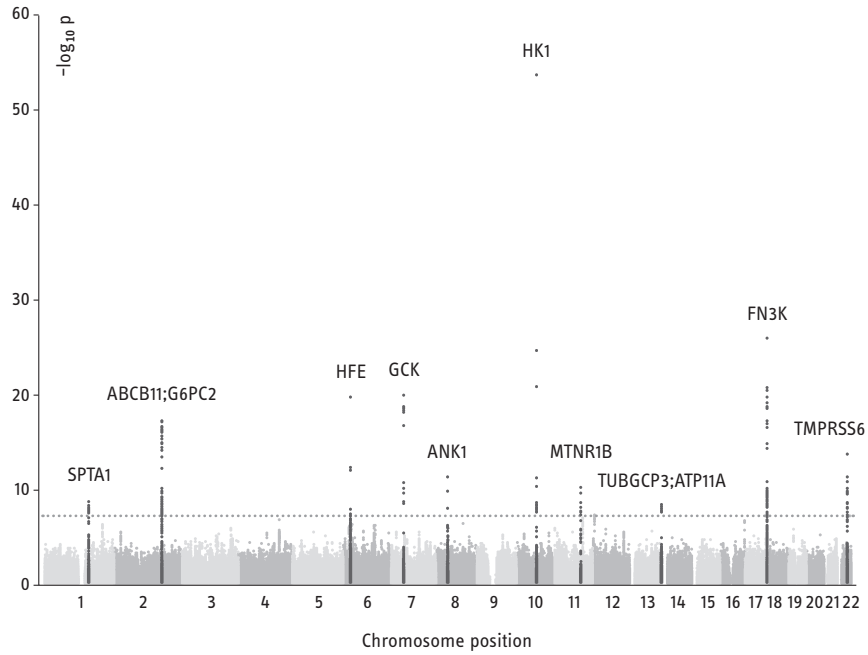
It is known that diseases such as chronic malaria or hemolytic anemia as well as blood transfusions, hereditary anemias and iron storage disorders can influence the variability of HbA1C. Although prior to this study some loci were known that influence the HbA1C level, the scientists assumed that far more genetic factors than previously known determine the concentration of HbA1C – otherwise the high heritability of the HbA1C value cannot be explained, which experts estimate at about 50 percent.

In a first step, the scientists analyzed 35 920 data sets from 23 cohorts, which contained the HbA1C level and genome-wide genetic data in the form of single nucleotide polymorphisms (SNPs). In a second part of the study, they analyzed the data of 10 000 additional individuals in eight cohorts to further verify the significance of the results of the genome-wide analysis.

Part of this global study was carried out in the KORA study under the responsibility of Christian Gieger together with H.-Erich Wichmann, head of KORA and director of the Institute of Epidemiology at Helmholtz Zentrum München.

The acronym KORA stands for Cooperative Health Research in the Augsburg Region. Overall, the scientists identified nine loci that modulate the concentration of HbA1C in the blood significantly. Six of these had previously not been associated with

Genome-Wide Meta-Analysis of HbA1C Levels



Manhattan plot of the 2.5 million genetic markers and the strength of their association with HbA1C shown in -log10 (P value)

the marker. Seven can be associated with hereditary diseases such as anemias and iron storage disorders. Common variants in these loci affect the biology of the red blood cells and make a small but measurable contribution to a diabetes diagnosis based on the HbA1C.

If the genetics of markers is known, they can be used to develop individual treatments for patients. The findings of this meta-analysis are a step toward providing better care for diabetes patients.

Different markers are used for the diagnosis and monitoring of diabetes. The glycated hemoglobin (HbA1C) test – commonly called the long-term blood glucose test – measures the average blood glucose concentration during the previous eight weeks. It determines the proportion of glucose bound to hemoglobin in the total hemoglobin circulating in the blood.

Original Publication
Nicole Soranzo et al.: Common variants at 10 genomic loci influence hemoglobin A1C levels via glycemic and nonglycemic pathways.
Diabetes 59 (2010) 3229-3239 | doi:10.2337/db10-0502

Passive Smoking Increases the Risk for Type 2 Diabetes

"In the future, more and more people will suffer from diabetes. That is why it is important to identify important risk factors such as active and passive smoking. We can thus develop preventive measures that not only take into account the individual patient, but the entire population."

People who are passively exposed to cigarette smoke develop type 2 diabetes more frequently than people who are not exposed to smoke. This previously unknown relationship was recently confirmed by a large epidemiological study.

PD Dr. Christine Meisinger

2008 Habilitation at Ludwig-Maximilians-Universität Munich — **since 2007** Head of the MONICA / KORA Acute Myocardial Infarction (AMI) Registry Augsburg — **since 2001** Head of the KORA Study Center Augsburg — **2000** Specialist in General Medicine

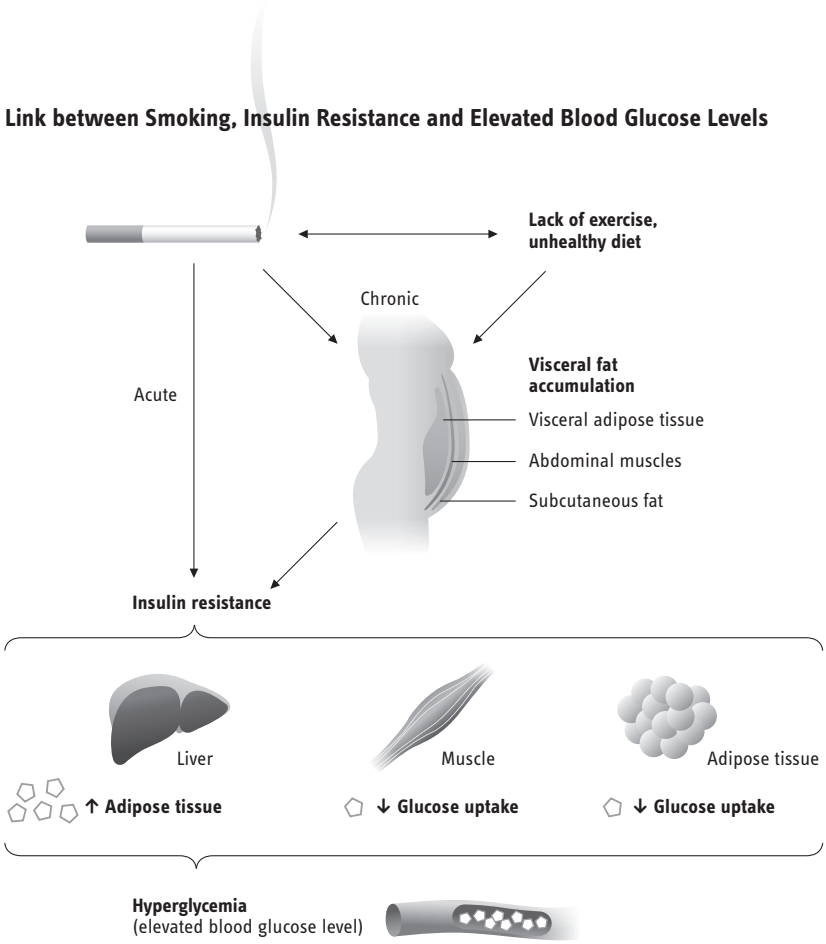
Cooperation Partners / Authors

German Diabetes Center, Düsseldorf Bernd Kowall, Wolfgang Rathmann, Klaus Strassburger, Margit Heier, Guido Giani — **Helmholtz Zentrum München** Rolf Holle, Barbara Thorand, Annette Peters, Christine Meisinger

Christine Meisinger and her research group had suspected that passive smoking might impact the development of type 2 diabetes mellitus just like active smoking does. In a follow-up study to verify their hypothesis, the scientists evaluated data which were originally collected within the scope of the KORA study (Cooperative Health Research in the Region of Augsburg) between 1999 and 2001.

Together with Wolfgang Rathmann, German Diabetes Center in Düsseldorf, Christine Meisinger had asked 1223 subjects between 55 and 74 years of age to take part in an oral glucose tolerance test (OGTT). This test is considered to be the gold standard of diabetes diagnosis in epidemiological studies. Seven years later, 887 of the subjects participated in a follow-up OGTT. At both time points in the study, the scientists asked the participants how many cigarettes they had smoked in the past and present, and how much smoke pollution they were exposed to at work and at home. At the time of the first oral glucose tolerance test, none of the study participants suffered from type 2 diabetes. Seven years later 93 people had developed the disease. Hence, the study confirmed the association known from epidemiological studies: Active smokers are more likely to suffer from diabetes than nonsmokers. In addition, for the first time the researchers were able to show the harmful effects of passive smoking. A comparison of the results at follow-up and at baseline showed that participants who inhaled passive cigarette smoke at work or at home were twice as likely to develop diabetes as participants who neither actively smoked nor inhaled smoke as passive smokers.

Link between Smoking, Insulin Resistance and Elevated Blood Glucose Levels



Smoking is associated with increased insulin resistance. The accumulation of visceral fat tissue may be partly explained by the frequent association between smoking, physical inactivity and unhealthy diet. In insulin resistance, the hormone insulin becomes less effective. The muscle and fat cells take up less blood glucose, and more glucose is released from the liver. Blood glucose levels rise.

This relationship was even clearer in a further analysis: Here, the scientists only examined the data of 238 so-called prediabetics. These included all study participants whose blood glucose level in the glucose tolerance test was higher than normal but still had not exceeded the threshold for diabetes. They developed diabetes even four times more often than active and passive nonsmokers.

These results remained constant even after other factors were considered: waist circumference, social status, parents with diabetes, age, gender and lifestyle. The study shows how behavior that increases the risk for specific diseases can be identified by means of epidemiological research with the aid of cohort studies. Thus, the smoking ban in public buildings and restaurants also helps prevent diabetes.

Type 2 diabetes can have various causes. Besides genetic predisposition, external risk factors such as overweight and physical inactivity can contribute significantly to the development of the disease. Epidemiological studies have shown that active smoking increases the risk of developing type 2 diabetes mellitus.

Original Publication
Bernd Kowall et al.: Association of passive and active smoking with incident type 2 diabetes mellitus in the elderly population: the KORA S4/F4 cohort study. Eur J Epidemiol 25 (2010) 393–402 | doi:10.1007/s10654-010-9452-6

Inflammation Enzyme Controls Energy Homeostasis

"The global increase in the number of obese people is a challenge for medicine. This challenge cannot be met without appropriate new treatments. The findings of our study provide starting points for developing a new weight loss method."

Dr. Jan Rozman

since 2006 Head of the Energy Metabolism Screen at the German Mouse Clinic, Helmholtz Zentrum München — **since 2008** Research associate of the Molecular Nutritional Medicine Unit of Technische Universität München — **2001–2006** Research associate, Philipps-Universität Marburg — **1998–2001** Postdoc, Zoology Department, La Trobe University, Melbourne/Australia

Prof. Dr. Martin Klingenspor

since 2007 Professor of Molecular Nutritional Medicine, Technische Universität München — **since 2001** Principal investigator at the Energy Metabolism Screen at the German Mouse Clinic — **2001** Habilitation — **1997–2006** Scientist and lecturer in the Department of Animal Physiology, Philipps-Universität Marburg, most recently deputy director — **1995–1996** Postdoc, Lipid Research Laboratory, West Los Angeles VA Medical Center, USA — **1994–1995** Postdoc in the Department of Animal Physiology, Philipps-Universität Marburg

Prof. Dr. Martin Hrabě de Angelis

since 2000/2003 Director and chair of the Institute of Experimental Genetics at Helmholtz Zentrum München and the Institute of Experimental Genetics at Technische Universität München — **since 2000** Director of the German Mouse Clinic and the European Mouse Mutant Archive — **1997–2000** Group leader of the research group Functional Genetics — **1994–1997** Postdoc, The Jackson Laboratory Maine, USA

Cooperation Partners / Authors

German Cancer Research Center Heidelberg Alexandros Vegiopoulos, Karin Müller-Decker, Daniela Strzoda, Iris Schmitt, Evgeny Chichelnitskiy, Anke Ostertag, Mauricio Berriel Diaz, Stephan Herzig — **Helmholtz Zentrum München and Technische Universität München** Jan Rozman, Martin Klingenspor, Martin Hrabě de Angelis — **Goethe University Frankfurt / Main** Rolf M. Nüsing — **Philipps Universität Marburg** Carola W. Meyer — **Université de Lausanne** Walter Wahli

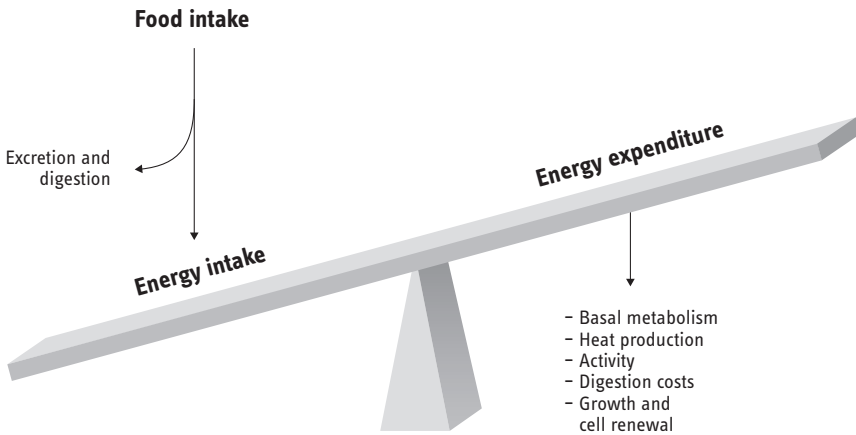
The inflammation enzyme cyclooxygenase-2 in mice stimulates the formation of brown adipose cells, which convert stored energy into heat. Mice with an increased enzyme production can keep the body's energy balance stable, according to a study by scientists of the German Mouse Clinic at Helmholtz Zentrum München and of the German Cancer Research Center in Heidelberg. Their finding is an important step forward in understanding energy homeostasis in the human body.

Special brown adipose cells are formed in the white adipose tissue of rodents if the temperature falls in their habitat. These fat cells are called brite (=brown in white) or beige adipocytes, and they play a key role in maintaining body temperature by generating heat. Jan Rozman of the German Mouse Clinic, together with colleagues of the German Cancer Research Center Heidelberg, Technische Universität München, Philipps-Universität Marburg and research centers in Frankfurt and Lausanne, has made a significant contribution to understanding the mechanism underlying the generation of these adipocytes.

The scientists focused their research on the inflammation enzyme cyclooxygenase-2, abbreviated Cox-2, which catalyzes the rate-limiting step in the synthesis of prostaglandins, which play an important role in the cascade of inflammation factors. As it turns out, Cox-2 is also an important factor in regulating energy homeostasis and significantly influences metabolism in fat tissue.

A comparison of Cox-2 formation in the white adipose tissue of obese mice or in mice with cancer cachexia showed no difference to that of control mice. However, if the mice were exposed to low ambient temperatures for four weeks, the quantity of synthesized mRNA in the abdominal white adipose tissue doubled. At the same time, the production of the so-called uncoupling protein Ucp1 increased. Ucp1 causes heat generation in the mitochondria by uncoupling ATP production from the respiratory chain. Here the food energy stored as fat is converted into heat. The scientists were also able to induce brown adipose cells artificially by treating the mice with an β-adrenergic agonist. Like in the experiment exposing the mice to cold, here, too, more Cox-2 and therefore more prostaglandin were generated.

Energy Balance



A positive energy balance leads to weight gain. Surplus energy intake can be compensated by increased activity or increased heat production

In a long-term experiment, the team of researchers compared Cox-2-deficient mice with mice exhibiting normal Cox-2 expression that were either fed a control diet or chow containing a Cox-2 inhibitor. The experiment clearly revealed that Cox-2-deficient animals were not able to regulate their energy homeostasis. Even when exposed to cold, the differentiation of brown adipose cells could not be induced. When Cox-2 was inhibited, the mice hardly formed any brown adipocytes at all.

The importance of Cox-2 to the overall energy balance has been demonstrated particularly by scientists in the Energy Metabolism Screen of the German Mouse Clinic. In mice with augmented Cox-2 production induced by a molecular biological trick, the researchers observed increased formation of brown adipose cells: The animals were leaner and had 20 percent less body mass than normal mice. Even with high-calorie chow they did not gain weight. Instead their body temperature rose and they expended more energy.

The results clearly show that Cox-2 and prostaglandins are crucial factors for the formation of brown adipocytes and for the regulation of body mass. The scientists estimate that as little as 50 grams of brown adipose tissue could boost the metabolic rate of the human body by 20 percent. This would reduce body mass by four kilograms within one year.

The body stores surplus energy obtained from food in white adipose tissue. Newborn babies (and also rodents) have so-called brown adipose tissue, which aids in keeping the body temperature constant. Recent studies have revealed that adult humans also have brown adipose tissue.

Original Publication

Alexandros Vegiopoulos et al.: Control of energy homeostasis in mice by de novo recruitment of brown adipocytes. Science 328 (2010) 1158-1161 | doi:10.1126/science.1186034

Structure Determination of Biomolecules in Their Natural Environment

"In order to investigate the spatial structures and molecular mechanisms of biomedically relevant protein complexes, we apply and optimize modern structural biology techniques – in particular, NMR spectroscopy. From this we hope to provide a new basis for modern structure-based drug research."

Researchers at Helmholtz Zentrum München and Technische Universität München have developed a new strategy to efficiently determine the spatial structure of protein in solution. The strategy is flexible and universally applicable for obtaining structural information on proteins and protein complexes.

Prof. Dr. Michael Sattler

since 2007 Director of the Institute of Structural Biology at Helmholtz Zentrum München and professor of Biomolecular NMR Spectroscopy at Technische Universität München — **1997–2006** Group leader of the research group Biomolecular NMR Spectroscopy at the European Laboratory for Molecular Biology (EMBL), Heidelberg — **1995–1997** Postdoc Abbott Laboratories, Abbott Park / Chicago, USA

Cooperation Partners / Authors

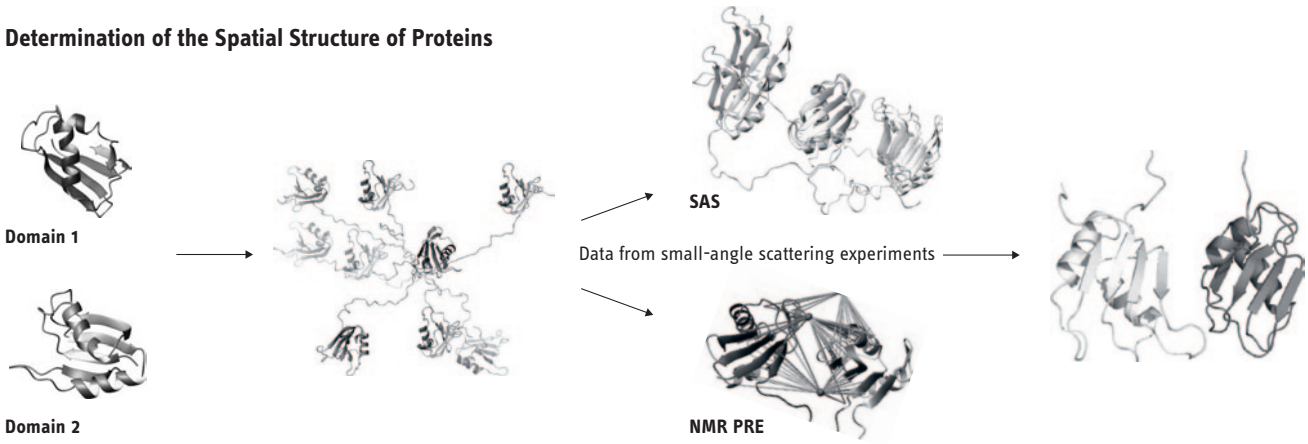
European Laboratory of Molecular Biology Heidelberg Bernd Simon — **Institut Européen de Chimie et Biologie, Pessac:** Cameron D. Mackereth — **Institut Pasteur, Paris** Michael Nilges — **Helmholtz Zentrum München and Technische Universität München** Tobias Madl, Michael Sattler

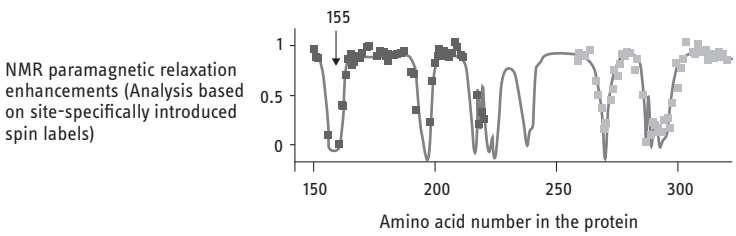
The researchers led by Michael Sattler combined several existing approaches to develop an efficient strategy for determining the spatial structure of biomolecules in solution. The strategy is based on biomolecular NMR spectroscopy.

Until now, the determination of the spatial structures of larger protein complexes in solution was very challenging and time-consuming. The new strategy consists of several steps. In the first step, the researchers collect existing structural information on the subunits of the protein complex that can be readily determined by conventional analytical methods. Then the relative orientation of these subunits to each other is determined by measuring so-called residual dipolar couplings with NMR providing information about the relative orientation of subunits. In the third step, the researchers introduce nitroxyl groups (molecules containing an unpaired electron) at various positions in the protein. These induce paramagnetic relaxation enhancements, enabling the scientists to measure distances between the subunits and thereby deduce the three-dimensional structure of the protein complex.

Sattler's team conducted the procedure on two structural domains of the human splicing factor U2AF65. Splicing factors are decisive in regulating gene expression and enable the formation of different proteins from a single gene. By combining the various NMR data, the scientists were able to calculate the structure of the tandem domains in solution. A different structure of U2AF65 was previously determined by x-ray structure analysis – which involves removal of water from the proteins via crystallization. As the new method analyzes proteins in solution it does not influence even weak interactions between the domains, and thus better reflects the structure of proteins in their natural environment in the cell. Using this new strategy, biological regulation mechanisms in which weak and transient interactions occur can be stud-

Determination of the Spatial Structure of Proteins





Four stage, NMR-based strategy for determining the spatial structure of biomolecules in solution: In the first step of the process existing structural information on the subunits is collected. In the next steps, researchers determine how these subunits are arranged spatially to one another.

ied efficiently. Such dynamic effects play an important role in the molecular determination of many biological processes. The new strategy can provide information about how metabolic processes take place and how diseases develop – and thus provide a basis for the development of new drugs.

Many proteins have a complex spatial structure, in which different compact subunits are linked to each other by flexible chains. This flexibility is important to regulate the interaction of protein molecules with each other or with reactant partners. To perform x-ray structure analysis, the protein molecules must be assembled into a rigid crystal lattice. To understand the function of proteins in their natural environment, their structure must therefore be elucidated using appropriate methods in solution, such as NMR spectroscopy that is used here.

Original Publication
Bernd Simon et al.: An efficient protocol for NMR-based structure determination of protein complexes in solution. Angew. Chem. 122, 2011–2014 (2010) | doi:10.1002/ange.200906147

Effective Diagnosis of Mitochondrial Diseases

"The genetic causes of rare metabolic diseases are being identified with increasing frequency. We anticipate that in just a few years our method will be established as a standard diagnostic procedure. Then we will be able to diagnose patients more efficiently and provide more effective treatment."

Dr. Holger Prokisch

since 2003 Group leader of the research group Mitochondrial Disorders, Institute of Human Genetics at Helmholtz Zentrum München and Technische Universität München — **1999–2003** Group leader of the research group Biogenesis of Mitochondria, Institute of Physiological Chemistry of Ludwig-Maximilians-Universität Munich (LMU) — **1998–1999** Postdoc, Institute of Physiological Chemistry of LMU

Cooperation Partners / Authors

Helmholtz Zentrum München: Arcangela Iuso, Jonathan Hoser, Thorsten Schmidt — **Helmholtz Zentrum München and Technische Universität München** Tobias B Haack, Katharina Danhauser, Birgit Haberberger, Thomas Meitinger, Hans-Werner Mewes, Holger Prokisch — **Goethe University Frankfurt** Valentina Strecker, Ilka Wittig — **CeGaT GmbH, Tübingen** Detlef Boehm, Saskia Biskup — **Carlo Besta-Istituto Di Ricovero e Cura a Carattere Scientifico (IRCCS) Foundation, Milan** Graziella Uziel, Eleonora Lamantea, Federica Invernizzi, Massimo Zeviani — **University of Oxford, John Radcliffe Hospital, Oxford** Joanna Poulton — **Munich Municipal Hospital** Boris Rolinski

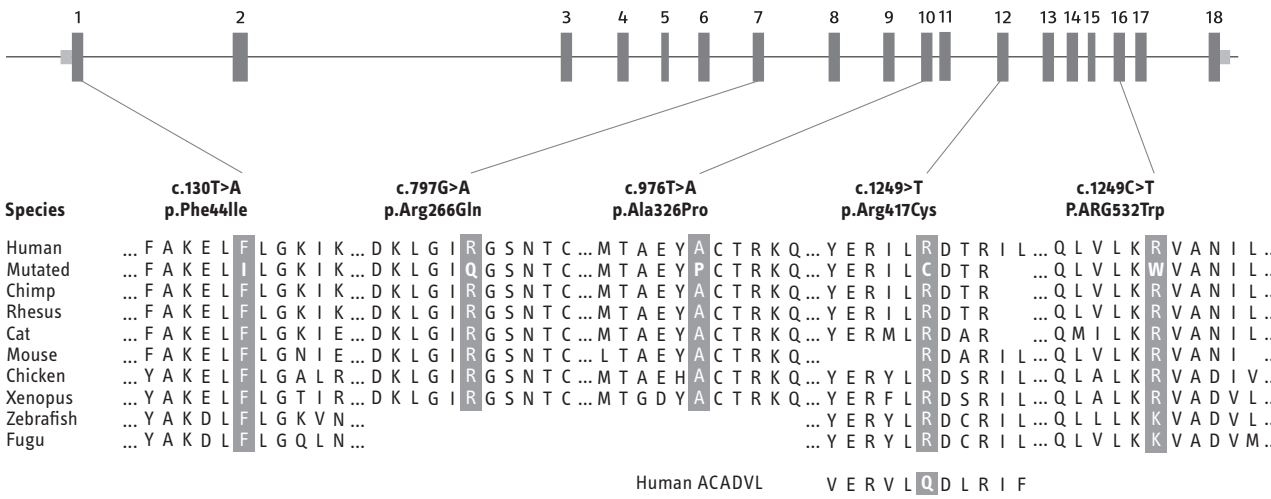
The genetic causes of mitochondrial defects can be detected by genomic analysis. The combination of exome analysis and functional cell assays enables efficient disease diagnosis and an early start of treatment.

The exome is the total of all coding sequences in the genome of an individual. Through exome sequencing, the genetic causes of rare hereditary diseases can be detected. Due to the high number of rare DNA variants each person carries, the analysis of exome sequencing data is difficult. Therefore usually several patients with the same disease characteristics are investigated. Working together with colleagues of Technische Universität München, Holger Prokisch's research group tested a new approach. They combined the sequencing of the exome of a single patient with a functional cell assay. Thus, for the first time, they were able to identify disease-causing mutations by analyzing a single genome.

The examined patient was the child of two healthy parents who were not related to each other. Shortly after birth the infant girl developed respiratory insufficiency and severe encephalopathy. In addition, she showed a marked lactic acidosis and cardiac involvement in the form of hypertrophic cardiomyopathy. Upon examination of cell samples from the liver, muscles and connective tissue, a profound complex I deficiency was detected in the mitochondrial respiratory chain. As cause of the symptoms the researchers identified the gene acyl-CoA dehydrogenase 9 (ACAD9), which previously had only been associated with lipid metabolism. To this end, they analyzed nearly 15 000 single nucleotide variants for new homozygous or compound heterozygous mutations. Among the corresponding proteins only ACAD9 was localized in the mitochondria. The examination of the patient's brother, who was also affected by the disorder, showed that he also had two mutations in the ACAD9 gene, while the healthy patients each had a heterozygous variant in the genome. Through the screening of 120 index cases with complex I deficiency, two additional patients with ACAD9 mutations were identified. Experiments in fibroblasts of the patient

ACAD9 Gene Structure and Mutations

The ACAD9 gene has 18 exons. Five different disease variants were discovered in ACAD9. A comparison of the ACAD9 protein sequence of different species shows a high correlation of the affected positions. This suggests that the found mutations are functionally significant.



confirmed the pathogenic nature of the mutation found in the infant girl and confirmed the importance of ACAD9 for complex I activity.

All sequence variants found in the ACAD9 gene are point mutations that lead to changes of conserved amino acid residues. This probably causes misfolding of the protein. Riboflavin acts as a co-factor of ACAD and supports the folding and stability of the protein. In fact, by giving the patients supplementary doses of riboflavin, the activity of the mitochondrial complex I could be increased.

The new method significantly improves molecular diagnostics and enables targeted therapies. Patients are already benefiting from the findings of the study – patients with ACAD9 mutations are now being treated with riboflavin. The new method is also important for the diagnosis of diseases such as Parkinson's and diabetes. In these diseases, too, improperly functioning mitochondria play an important role.

Disorders of the respiratory chain of mitochondria cause serious clinical pictures. In a defect of the mitochondrial complex I, fewer electrons are transported into the mitochondria, and therefore the cells do not get sufficient energy. Tissues with high energy demand, such as the brain, heart, muscles and endocrine organs are particularly affected.

Original Publication
Tobias B. Haack et al.: Exome sequencing identifies ACAD9 mutations as a cause of complex I deficiency. Nature Genetics 42 (2010) 1131-1134 | doi:10.1038/ng.706

Newly Discovered Gene Contributes to Regulation of Cilia Disassembly

"The research on cilia has tremendous potential for health research. An increasing number of hereditary diseases in recent years have been linked to cilia dysfunction, and there are indications that common diseases such as diabetes or obesity are also associated with them. Our work provides a valuable knowledge base to understand the causal relationships and to develop new therapeutic approaches."

With the discovery of the Pitchfork gene, scientists of Helmholtz Zentrum München have identified one of the first proteins governing cilia disassembly at the beginning of cell division. Defects in this gene lead to cilia dysfunctions responsible for developmental disorders in the body and severe heart failure. The studies are an important step towards a deeper understanding and a more detailed classification of ciliopathies.

Dr. Heiko Lickert

2009 European Research Council Starting Grant for the Study of Ciliopathies — **since 2009** Group leader of the research group Endoderm Development and Regeneration, Institute of Stem Cell Research, Helmholtz Zentrum München — **2005–2009** Emmy Noether Junior Research Group, Institute of Stem Cell Research, Helmholtz Zentrum München — **2003** Otto Hahn Medal — **2002** Hans Spemann Award — **2002–2004** Postdoc, Mount Sinai Hospital, Toronto — **2002** Postdoc, Max Planck Institute of Immunobiology and Epigenetics, Freiburg

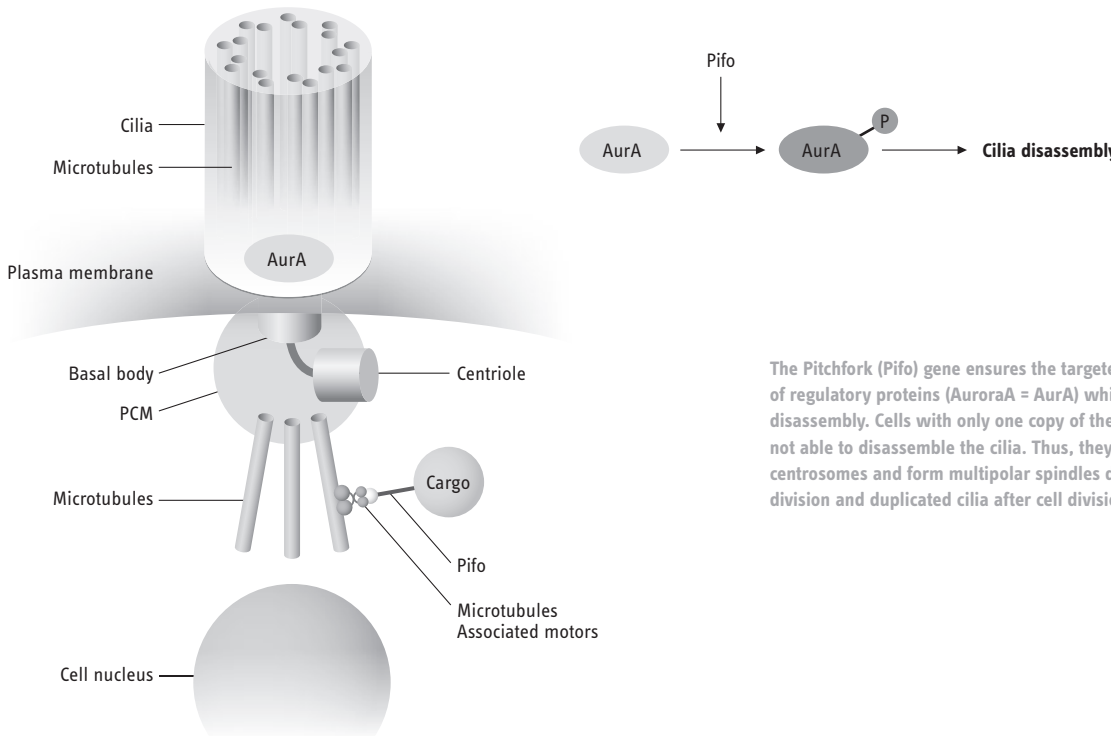
Cooperation Partners / Authors

Helmholtz Zentrum München Doris Kinzel, Heiko Lickert, Ingo Burtscher, Wolfgang Wurst, Dietrich Trümbach — **Helmholtz Zentrum München and University of Tübingen** Karsten Boldt, Marius Ueffing, John Hopkins University, Baltimore, Erica E. Davis, Bill Diplas — **INSERM, Paris** Tania Attié-Bitach — **John Hopkins University, Baltimore and Duke University, Durham** Nicholas Katsanis

Cilia are slender protuberances about five to ten micrometers (µm) long that are anchored by a basal body on the surface of almost all body cells. Like an antenna, they regulate the transmission of signals between cells. Although the serious consequences of defects in cilia structure have only been recognized in recent years, they are believed to be a causal factor in more than 30 diseases. Until the present study, however, the consequences of failure in cilia disassembly were largely unexplored.

A research team led by Heiko Lickert of the Institute of Stem Cell Research has now shown that also correct cilia disassembly is a decisive factor in governing healthy development. In the mouse embryonic node the scientists uncovered one of the first genes that play a key role in this process. If only one copy of the gene is defective, forked cilia develop, which is why the gene was named Pitchfork. At the beginning of mitosis, it ensures the directed transport of regulatory proteins to the basal body. In Pitchfork mutant cells, this results in an overreplication of centrosomes and faulty mitotic apparatus machinery. Thus, during mitosis the genetic material can no longer be distributed correctly; due to the amplified basal bodies double or forked cilia develop.

Pitchfork Regulates Cilia Disassembly



The Pitchfork (Pifo) gene ensures the targeted transport of regulatory proteins (AuroraA = AurA) which initiate cilia disassembly. Cells with only one copy of the gene are not able to disassemble the cilia. Thus, they overproduce centrosomes and form multipolar spindles during cell division and duplicated cilia after cell division.

Since cilia govern left-right assembly in the body, the consequences for embryonic development are serious. This leads to congenital heart defects and thus to cardiac insufficiency. In fact, Lickert and his team observed that mouse embryos with a defective Pitchfork gene died of massive heart defects. Analysis of the patients' DNA revealed that mutations in the PITCHFORK gene led to a similar clinical picture in humans – suggesting that this gene was indeed a new ciliopathy gene.

The researchers see links to other diseases as well. There are strong indications that problems in cilia disassembly can lead to tumor formation – here, too, the cause is overreplication of centrosomes and uncontrolled distribution of genetic material during mitosis, suggesting an association between cilia dysfunction and cancer. Another interesting aspect of the research results: The Pitchfork gene is only found in vertebrates. As a follow-up of this study, the researchers want to show that the Pitchfork gene represents an evolutionary adaptation for the Sonic hedgehog signaling pathway, which – only in vertebrates – depends on cilia function.

The term ciliopathy refers to diseases related to a loss of function of cilia affecting a variety of organs such as the kidneys, the lungs, the pancreas and the central nervous system. Furthermore, ciliopathies influence fundamental developmental processes such as the left-right asymmetry of the body and organ development.

Original Publication

Doris Kinzel et al.: Pitchfork regulates primary cilia disassembly and left-right asymmetrie. Developmental Cell 19 (2010) 66-77 | doi:10.1016/j.devcel.2010.06.005

Therapy

Antibodies against Cancer

From Research to Successful Application

1966
The Institute of Hematology develops immunological principles for bone marrow transplantation

1970
The Department of Immune Hematology is established

1975
First successful bone marrow transplantation in Germany

1977
Clinical use of T-cell depletion

1977
The Institute of Clinical Hematology is founded

1979
Purging of leukemia cells enables first autologous bone marrow transplantation

The Future

The immunological memory is strengthened by new active principles against tumor diseases

1994
Founding of the clinical cooperation group Bispecific Antibodies

2009
The first bispecific trifunctional antibody, based on immunological research conducted at the Center, is approved by the European Medicines Agency

1992
First studies on artificially produced antibodies for tumor therapy by the Institute of Immunology

1998
Founding of the company TRION Pharma GmbH

1998
TRION Pharma acquires licenses for antibody family and production method

1988
Adoptive immunotherapy is carried out successfully for the first time

1997
Global patent for a production and purification method for intact bispecific antibodies

1988
The Hematologikum is built on the premises of the University Hospital Grosshadern

1956
The British hematologists and radiation biologists David W. Barnes and John F. Loutit describe the graft versus host disease (GVHD) as a “secondary disease” induced by radiation sickness.

1957
The American doctor E. Donnall Thomas is the first to successfully perform an allogeneic bone marrow transplantation, for which he is awarded the Nobel Prize in Medicine in 1990.

1961
Jean Dausset, the French hematologist and later Nobel Laureate in Medicine discovers human leukocyte antigens (HLA).

1975 —

Center scientists perform the first successful bone marrow transplantation in Germany and develop adoptive immunotherapy, which later becomes a standard antitumor treatment.

— Future Vision

The immune system is harnessed and strengthened to fight cancer more effectively.

Enabling the Immune System to Fight Cancer

In 1975 Munich scientists and physicians performed the first successful bone marrow transplantation in Germany. Immunological research groups of what is now Helmholtz Zentrum München were largely responsible for establishing bone marrow transplantation in combination with radiation and chemotherapy as standard treatment for various diseases of the hematopoietic system. Today, immunotherapeutic strategies against cancer diseases are being developed further at the Center in the laboratory and in clinical trials.

In the 1960s, researchers of the Center began investigating bone marrow transplantation as a possibility for treating various diseases of the hematopoietic system. By 1975 they had succeeded in creating the preconditions for the first successful bone marrow transplantation in Germany. Together with doctors of the Munich-Schwabing Hospital, Professor Dr. Hans-Jochem Kolb succeeded in curing an eight-year-old boy who suffered from severe aplastic anemia.

T-cell depletion made its global debut as clinical method in 1977 and has since become an established standard treatment.

Scientists and physicians of the Center, the Munich-Schwabing Hospital and the two Munich universities joined together in the Munich Bone Marrow Transplantation Working Group to develop the treatment method further and to find new approaches to overcoming immunological complications. The Institute of Immunology under the direction of Professor Dr. Stefan Thierfelder developed the method of T-cell depletion, which made its global debut as clinical method in 1977 and today is an established standard treatment. In this method, prior to transplantation, the T cells are removed from the donor's bone marrow by means of antibodies. Thus, the immune reaction triggered by the transplantation is weakened – the graft versus host reaction is prevented or reduced.

The immunogenetic evaluation of tissue compatibility characteristics, the prerequisite for any form of bone marrow donation, is based on research work conducted at the Institute of Immunology. To date, eight tissue compatibility characteristics have been defined, in particular the human leukocyte antigens (HLA).

In 1979 a method for purging leukemia cells from the bone marrow was introduced, also based on research conducted at the Center, which enabled autologous transplantation. In this method, cells of the patient's own bone marrow are harvested during a remission phase – the tumor cells still present are deactivated with an antibody serum. After the patient has undergone whole-body radiation therapy, the patient's own serum-treated bone marrow graft is transplanted back into the patient.

In the late 1980s Professor Dr. Hans-Jochem Kolb and his colleagues of the clinical cooperation group Hematopoietic Cell Transplantation at Helmholtz Zentrum München and Ludwig-Maximilians-Universität Munich developed the method of adoptive immunotherapy, which utilizes the "tolerance" of the patient toward the donor bone marrow. In 1988 the researchers for the first time successfully treated a transplanted patient with relapsed leukemia by administering T cells of the bone marrow donor.

The targeted use of T cells against tumor cells is also the basis of new immunotherapeutic approaches pursued by the Institute of Molecular Immunology and the Institute of Virology at Helmholtz Zentrum München as well as by clinical cooperation groups, which the Center founded together with the Munich universities as clinical partners. The new therapies are intended to specifically program the immune system for the attack of tumors. In the laboratory and in part already in clinical trials, various strategies are being developed for utilizing specific T cells and for immune control of tumors.

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The combined bone marrow transplantation and blood stem cell transplantation is today an established method for treating aplastic anemias, innate immune defects, leukemias, malignant lymphomas and other tumors. Following radiation therapy or chemotherapy the patient receives the bone marrow from a donor who is as compatible as possible (allogeneic transplantation).

In autologous transplantation, the patient's own bone marrow is purified from malignant cells by means of antibodies before the marrow is transplanted back into the body. In 2001 approximately 3500 autologous and allogeneic bone marrow transplantations were carried out, as well as transplantations of peripheral stem cells. In 1993 the number was approximately 1100.

"Immunological approaches will enable us to improve the quality of life of cancer patients. In the immediate future we will have learned how the immune system recognizes tumor cells and how we can strengthen the immune response. Using immune cells that have been manipulated to target the individual tumor, we will be able to provide a more effective and gentle treatment against cancer."

Prof. Dr. Dolores Schendel ——

is the director of the Institute of Molecular Immunology at Helmholtz Zentrum München. Her institute has initiated several clinical trials based on the molecular and cellular principles of antitumor immunity and T-cell recognition.

1948
The Swedish immunologist Astrid Fagraeus describes antibody secretion by plasma cells.

1961
The English biochemist Rodney Porter elucidates the structure of antibodies, for which he receives the Nobel Prize in Medicine in 1972.

1975
Two biologists, the German Georges Köhler and the Argentine César Milstein, discover the principle of monoclonal antibody production using the hybridoma technique, for which they are awarded the Nobel Prize in 1984.

2009 —

The first therapeutic antibody against cancer "made in Germany" is approved by the European Medicines Agency. It is based on immunological research conducted at Helmholtz Zentrum München.

— Future Vision

Antibodies induce an immunological memory directed against tumor cells.

Cancer Therapy with Antibodies "Made in Germany"

The prototype of a new generation of immunotherapeutically effective antibodies that can target cancer cells was approved in 2009 by the European Medicines Agency (EMA). Marketed under the trade name Removab, this bispecific trifunctional antibody can be used in the treatment of malignant ascites, an accumulation of fluid in the abdomen caused by tumor diseases. The production method and the underlying active principle were developed, patented and out-licensed at what is today Helmholtz Zentrum München.

Due to progress made in the field of immunology and related technologies it became conceivable to artificially produce biological agents – such as antibodies – and to use these in therapy. Early in the 1990s the Institute of Immunology headed by Prof. Dr. Stefan Thierfelder began studying artificially produced antibodies in tumor therapy. Along with research on bone marrow transplantation, Thierfelder's institute studied antibodies which can bind to two cells simultaneously, so-called bispecific antibodies. From 1994 on, these studies were carried out in the clinical cooperation group Bispecific Antibodies led by Dr. Horst Lindhofer.

Removab is the first approved therapeutic antibody "made in Germany" and is considered to be a prototype for further antibodies.

By 2002 the researchers had elucidated the underlying active principles and production techniques of the novel antibodies. One of the results was a globally patented production and purification method with which it was possible for the first time to produce intact bispecific antibodies cost-effectively and in large quantities. This technique laid the basis for moving forward with establishing the necessary standards for the further development, clinical trial and finally the industrial production of the drug.

In 1998 the scientist Horst Lindhofer founded the company Trion Pharma GmbH. His company acquired the licenses for the antibody family developed at the Center as well as for the exclusive user rights to the biotechnological production method. Ascenion, the Center's marketing agency for research results, received a minimum license for this as well as shares in the company. Trion entered a cooperation agree-

ment with Fresenius Biotech GmbH, a subsidiary of the Fresenius group, in order to carry out clinical trials and to have a competent marketing partner.

Within the framework of this alliance, the novel antibody was developed, tested and guided through all regulatory procedures. Removab is the first approved therapeutic antibody "made in Germany" and is considered a prototype for further antibodies to treat breast cancer, B-cell lymphoma and malignant melanoma.

The target structure of the new therapeutic antibody is the transmembrane protein EpCAM – the acronym for epithelial cell adhesion molecule. It is produced particularly frequently and in highly elevated numbers by tumor cells. In different clinical studies it has already been tested as target structure for potential cancer drugs.

The special advantage of the trifunctional bispecific antibodies is that they recognize three targets: the cancer cell and two different kinds of immune cells – T cells and macrophages – which attack the tumor cells each in their own way. Because the two immune cells are brought very close together, the T cells are activated particularly efficiently; at the same time, via the macrophages they attract additional immune cells. Moreover, via these macrophages, they induce a long-term immunological memory. Thus, a new, extremely potent active principle is available which can be expanded to treat other cancer diseases.

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Bispecific antibodies have two different binding arms. They are produced artificially and are promising substances for use in cancer immunotherapy. Bispecific antibodies recognize an antigen, a target molecule on the surface of tumor cells, and also molecules on various effector cell types of the endogenous immune system. These are targeted and activated specifically, inducing them to target the tumor tissue.

"Trifunctional bispecific antibodies bring about a long-term immunological memory. In order to expand this highly potent active principle to include the treatment of additional cancer diseases, antibodies need to be produced that are targeted toward different other tumor antigens as recognition structures. A combination of this approach with other therapy strategies is also conceivable. In this way, it will be possible to at least slow the progression of cancer diseases over relatively long periods."

Prof. Dr. Ralph Mocikat ——

is the deputy director of the Institute of Molecular Immunology and also a research group leader. His research activities focus on how tumor cells escape from an attack by the immune system and how these mechanisms can be used for new therapies.

500 B. C.
The Greek physician Parmenides describes the healing effect of fever: “Give me the power to produce a fever and I will cure any illness.”

1886
The German surgeon Wilhelm Busch publishes studies on healing malignant tumors with artificially produced fever.

1962
The Italian Frederico Ritossa discovers the heat-shock protein in the fruit fly Drosophila melanogaster.

1986 —

A clinical research group at the Center develops a successful concept for treating malignant soft tissue tumors.

— Future Vision

The concept is further developed into a strategy for treating other forms of cancer.

Tumor Hyperthermia for Cancer Treatment

A clinical research group at the Center succeeds in introducing hyperthermia as innovative treatment option for malignant soft tissue tumors. In 2007 the results of the world's first randomized phase III trial were presented, confirming the effectiveness and the superiority of the combined treatment method in comparison to chemotherapy alone. The therapy, developed as a supplementary treatment option, gives the patients a significant increase in survival time and quality of life.

That treatment with hyperthermia can have a positive impact on healing diseases has been known since antiquity. As early as the 19th century there were experiments to cure cancer by inducing fever. Since 1986, the Center has been investigating whether hyperthermia can be limited to a localized region and has conducted studies on how cancer therapy can benefit from regional deep hyperthermia. The research team led by Prof. Dr. Rolf Issels is focusing on the effectiveness of combination therapy on sarcomas, i.e. soft tissue and bone tumors arising from connective and supporting tissue. In combination therapy, chemotherapy and hyperthermia are applied before and after surgical resection. The hyperthermia is only applied regionally and limited to the tumor and surrounding infiltrated tissue. Since 1993 regional deep hyperthermia has been carried out as a treatment method within the scope of a model plan of the health insurance companies. In 1999 a clinical cooperation group was established with University Hospital Grosshadern. Apart from the clinical application, this group is investigating the underlying immunological and cell biological mechanisms. Elevated body temperatures such as are produced by hyperthermia in a limited region put the cells under stress. Thus, heat-shock proteins (HSP), also called stress proteins, are induced into the tumor. They attack the cells' innate immune system in various ways, for example by marking the tumor cells, thus making them recognizable targets for the killer cells of the immune system.

Since 1993 German health insurance companies have approved hyperthermia as a method of treatment.

The world's first randomized phase III study, completed in 2007, showed that this innovative form of therapy can improve the outcome of sarcoma patients significantly. The ten-year study confirmed the effectiveness of regional hyperthermia in

combination with chemotherapy for deep-lying high-risk soft-tissue sarcomas in more than 300 high-risk patients. For those patients who were treated in addition to surgical removal and radiotherapy of the sarcoma with a combination of chemotherapy and regional deep hyperthermia, a significant improvement in tumor response and disease-free survival was observed. For one-third of the patients, this combination therapy was started before the operation. Patients who had undergone combined regional hyperthermia therapy and chemotherapy subsequently had a post-treatment disease-free survival time that was on average 14 months longer than the survival time of patients treated with chemotherapy alone. In addition, 20.6 percent of the patients only treated with chemotherapy showed local tumor growth during the pre-operative treatment, but only 6.8 percent of the patients with combination therapy did so. The study showed that if regional hyperthermia and chemotherapy are combined, the risk for the tumor to continue to grow uncontrolled at an early stage is much lower. At the same time, the chance for the tumor to shrink in size is much greater. Patients who completed the prescribed combined treatment protocol showed also significant improvement of their overall survival compared to the chemotherapy alone population.

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In regional deep hyperthermia tumors are heated with electromagnetic waves up to 40 to 44 degrees Celsius. At temperatures higher than 42 degrees the cells begin to die off due to the heat. Combination therapy utilizes the fact that tumor cells above 40 degrees are more responsive to defense processes of the immune system and to radiation therapy and chemotherapy.

"The fact that we could confirm the benefit of regional hyperthermia for sarcomas as 'proof of concept' demonstrates the importance of the symbiosis of basic and clinical research. Now is the time to conduct comparative clinical trials to determine whether supplementing the standard treatment with regional hyperthermia shows promise in fighting additional forms of cancer."

Prof. Dr. Rolf Issels —

is head of the clinical cooperation group Hyperthermia at Helmholtz Zentrum München and Ludwig-Maximilians-Universität Munich. He has received numerous medical awards for developing and implementing regional deep hyperthermia as an innovative treatment approach.

1916
Albert Einstein postulates the existence of stimulated emission of light – the physical basis of the laser.

1954
The U.S. physicist Charles H. Townes develops a device for amplifying and producing electromagnetic waves by stimulated emission – the maser.

1960
The U.S. physicist Theodore Maiman constructs the first functioning laser – a ruby laser.

1970 ——
Researchers of the Center give important impulses for the medical use of lasers.

—— Future Vision

Methods created at the Center are developed further into clinical applications.

Basic Principles for the Use of Lasers in Medicine

In the 1970s the Department of Applied Optics developed the physical principles for the successful application of lasers in medicine. In close collaboration with physicians at Bavarian university hospitals, new methods of treatment in the fields of dermatology and urology were developed and transferred into routine clinical use.

Shortly after the development of the first laser by the American Theodore Maiman, the new light source was tested for its medical usefulness. The pioneer field was ophthalmology, in which the ruby laser was used for coagulation therapy for retinal detachment. The first patients were treated in 1962.

In 1964 a LASER working group at the Center built the first experimental system for laser applications in the biomedical field. In 1970 the Department of Coherent Optics was founded to explore the application of holography and the laser to medical-biological problems. The Department was headed by Prof. Dr. Wilhelm Waidelich, who had already begun studying medical laser applications in 1963 at the Technical University of Darmstadt. Early in the 1970s research activities focused on basic research regarding the biological effects of laser radiation, especially on the interaction of laser radiation and tissue. Another focus of the Department was on developing the basic physical principles of lasers for diagnostic and scientific purposes. The sharp focus that can be achieved with laser beams enables the quantitative analysis of even very small samples. Laser microprobes rely on this principle to detect, for example, substances in bacterial structures, components in smoke particles and mineral inclusions. In 1971 a laboratory model of a laser microprobe for the analysis of inorganic ions at the subcellular level was built. In 1974 a patent application for a method for the automatic focusing of microscopic specimens was filed. In 1976, this work resulted in a prototype, developed in cooperation with an industrial partner.

In focal laser photocoagulation, argon laser light is used to coagulate small blood vessels.

In 1977 Department scientists presented an innovative technique for the microdissection of frozen tissue sections, allowing contactless preparation of specimens from tissue samples. The areas to be examined were first marked with a low-energy laser and then cut out with an adaptable UV laser.

The same year the Department introduced a new method for automatic evaluation of cytological specimens. It was designed for use in cancer detection examinations for the prescreening of atypical cells. In 1981 a first test system was assembled for use under real practice conditions. Also in 1977 the Center filed a patent application for a rapid automatic procedure for measuring blood sedimentation rates. It shortened the time needed to determine blood sedimentation values from two hours to just a few minutes. The Federal Minister of Research at that time, Hans Matthöfer, lauded the new development at a technology trade show as a promising example of cost reduction opportunities in health care.

Helmholtz Zentrum München and the research location Munich have given important impulses for the development of medical laser applications. Many of the methods developed here have been successfully transferred into medical applications, and further research activities have been transferred to the clinics.

In order to determine radiation protection limits for the use of lasers, a project on potential eye injury was initiated in 1972. The aim was to create a basis for safety recommendations and legal regulations.

In the mid-1970s the researchers also began to specifically investigate how laser applications developed in the laboratory could be transferred into clinical practice. In 1976, in collaboration with dermatologists, laser procedures were used for the first time to treat patients with skin diseases due to vascular anomalies. The method of focal laser photocoagulation was developed: here argon laser light is used to coagulate small blood vessels.

Clinical laser applications were the focus of the Central Laser Laboratory, established in 1973 with special funds of the Federal Ministry of Research and Technology (BMFT), today the Federal Ministry of Education and Research (BMBF). In this laboratory new uses for laser-based techniques were developed and transferred into clinical trials. These included endoscopic hemostasis techniques for gastrointestinal hemorrhage, which were tested for the first time in 1977. In particular, the researchers also developed techniques for selective tumor labeling with compounds that accumulate in tumor tissue and fluoresce when illuminated by a laser source. At the same time the light sensitivity of the tumor tissue is increased, enabling the selective destruction of the tumor when illuminated by a laser. Corresponding methods are currently used in clinical practice, e.g. for the treatment of bladder tumors.

In the mid-1970s medical laser working groups were established at hospitals in the Munich region in the fields of urology, gastroenterology, ophthalmology, neurosurgery and gynecology. In 1976 these groups joined together to form an association that gave important impulses for medical laser research and applications in Germany.

Many of the laser applications the Neuherberg researchers helped to develop were successfully transferred into clinical applications; for the participating scientists the focus of research activity shifted to the clinics. After the founding of an own laser center in the mid-1990s in the University Hospital Grosshadern, the last remaining laser working group in Neuherberg discontinued its work at the end of 1995.

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Lasers produce light by stimulated emission. In appropriate materials atoms or molecules are put into an excited state by supplying energy. The excited particles emit photons which interact with other particles, stimulating the emission of additional photons that match exactly in wavelength, phase and direction of radiation. The radiation is amplified by a resonator and exits through a semitransparent mirror. The exiting beam is narrow and focused and thus has a high energy density per unit area.

Medical laser procedures are currently used in dermatology, angiology, surgery, gynecology, urology, pulmonology, orthopedics, neurosurgery, ophthalmology and oncology.

Prof. Dr. Dr. Fabian Theis
works on mathematical models for molecular networks. For his concepts for the enhancement of existing models in systems biology, the European Research Council awarded him a Starting Grant in 2010. During the next five years he has around 1.25 million euros at his disposal to conduct his research. As an example of application, Theis intends to demonstrate which genetic factors interact in the development of embryonic stem cells into differentiated tissue.

Head of the junior research group at the Institute of Bioinformatics and Systems Biology at Helmholtz Zentrum München and Professor for Mathematics in Systems Biology at Technische Universität München — **2008** Postdoctoral qualification ("Habilitation") in Biophysics at the University of Regensburg — **2006–2007** Bernstein-Fellow at the Bernstein Center for Computational Neuroscience in Göttingen — Research grants for work in Japan, USA, and Finland — Co-founder of Instant Solutions, a company for the development of web-based database applications — **2003** Ph.D. in Computer Science — **2002** Ph.D. in Physics — MSc degrees in Mathematics and Physics at the University of Regensburg — Born **1976** in Ansbach

since 2009 Member of the "Young Academy" at the Berlin-Brandenburg Academy of Sciences and Humanities and the German Academy of Natural Scientists Leopoldina — **2006** Recipient of the Heinz Maier-Leibnitz Award of the German Research Foundation (DFG)

Understanding Networks

Starting Grant from the European Research Council for

Fabian Theis

“Based on the theoretical models of systems biology, we derive hypotheses for new experiments, which in turn improve the accuracy of the models. These models help us to better understand biological networks. Thus, complex processes such as the differentiation of stem cells can be understood. In cooperation with other disciplines, this will bring us closer to an effective cell replacement therapy.”

Neuropsychiatric Research

at Helmholtz Zentrum München since 1960

1964
The Institute of Biology researches mechanisms of action of radiation-induced reactions on the nervous system.

1968
Properties of nerve cells researched

1990
Research into the effects of indoor chemicals, inter alia on the nervous system, lead to stricter statutory regulations

1998
First KORA survey to gather data on the significance of cardiovascular and genetic risk factors for senile dementia

1998
As part of the German Human Genome Research Project, researchers at the Center develop a mouse model for alcoholism

1999
The Center begins its genetic research on the development of the nervous system

2000
Using the mouse mutant Beethoven, researchers at the Center develop a model for investigating age-related deafness

2004
Expansion of research into neurodegenerative diseases through the foundation of the first Institute of Stem Cell Research in Germany

The Future

By elucidating complex interdependencies, the Center lays the foundations for innovative therapies, diagnostic procedures and preventive strategies for combatting neuropsychiatric diseases

2010

Magdalena Götz receives the Order of Merit of the Federal Republic of Germany for researching the molecular fundamentals of brain development

2010

Proteins relevant to Parkinson's disease are successfully identified in various studies

2007

Magdalena Götz receives several science awards for her research on the differentiation of nerve cells

2009

Helmholtz Zentrum München becomes a partner of the German Centre for Neurodegenerative Diseases (DZNE)

2006

Researchers of the Center present initial results of a systematic neurology screen at the German Mouse Clinic

2008

As part of the Helmholtz Alliance "Mental Health in Old Age", the Center researches neurodegenerative diseases

2009

Researchers at the Center identify a genetic risk factor for Parkinson's disease

2008

By identifying risk genes for the Restless Legs Syndrome, researchers at the Center provide the basis for cause studies of the disease

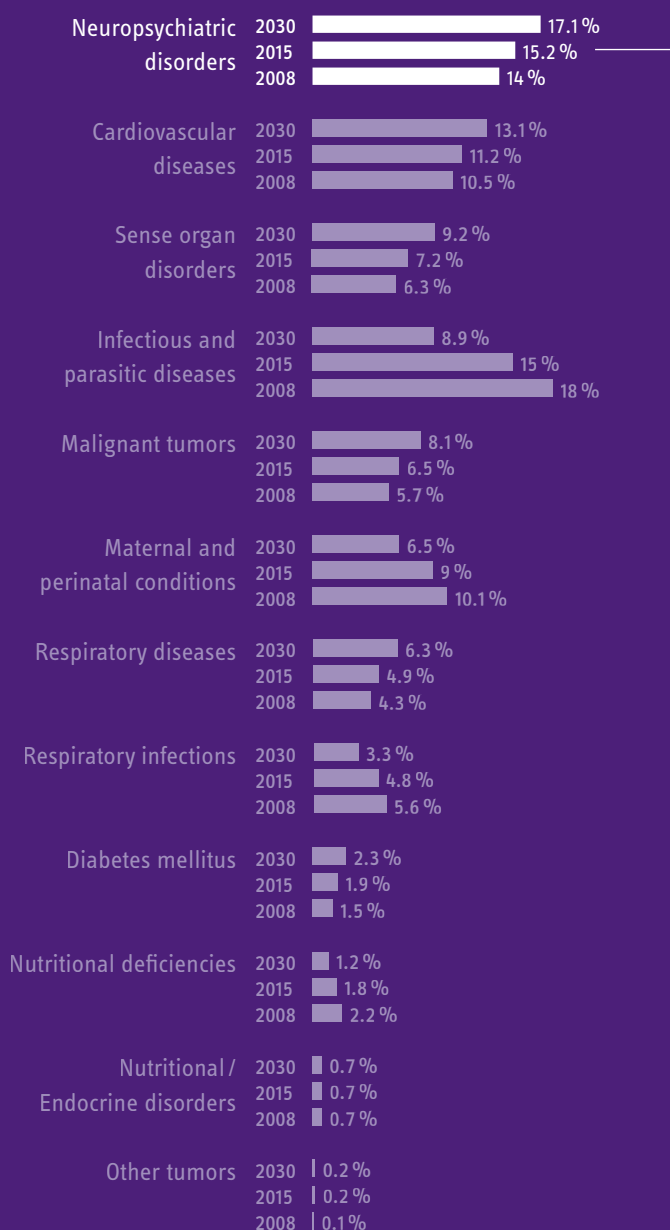
2005

The Institute of Stem Cell Research identifies molecular mechanisms of nerve regeneration in the adult brain

Partner of the German Centre for Neurodegenerative Diseases (DZNE)

Helmholtz Zentrum München

Causes of the Global Burden of Disease: Neuropsychiatric Diseases Increase Dramatically



	2008	2015	2030
Unipolar depressive disorders	4.7 %	5.3 %	6.2 %
Bipolar affective disorders	1.0 %	1.1 %	1.1 %
Schizophrenia	1.2 %	1.2 %	1.3 %
Epilepsy	0.5 %	0.5 %	0.5 %
Alcohol use disorders	1.7 %	1.7 %	1.9 %
Alzheimer and other dementias	0.8 %	1.0 %	1.4 %
Parkinson's disease	0.1 %	0.1 %	0.2 %
Multiple Sclerosis	0.1 %	0.1 %	0.1 %
Drug use disorders	0.6 %	0.6 %	0.7 %
Post-traumatic stress disorder	0.2 %	0.3 %	0.3 %
Obsessive-compulsive disorders (OCD)	0.4 %	0.4 %	0.5 %
Panic disorders	0.5 %	0.5 %	0.6 %
Insomnia	0.3 %	0.3 %	0.4 %
Migraine	0.5 %	0.5 %	0.6 %

These projections show the share of the overall burden of disease in percent, stated in DALYs.

One DALY (Disability Adjusted Life Year) is a year of healthy life lost to disability. The "DALY" figure aims to not just summarize the mortality, but also the impairment of the normal life, free of complaints, through an illness, by providing a comparable measure.

Source: Projections of mortality and burden of disease, world health organisation, baseline scenarios 2008, 2015, 2030
www.who.int/healthinfo/global_burden_disease/projections/en/index.html

The **German Centre for Neurodegenerative Disease** was newly established in 2009 as a Research Unit within the Helmholtz Association. Scientists at eight locations conduct research into the causes and mechanisms of neurodegenerative diseases, their diagnoses and therapies. The main center is located in Bonn. Helmholtz Zentrum München is one of the cooperation partners in Munich and as such involved in the research fields and goals of the German Centre for Neurodegenerative Diseases.

"As a partner of the German Centre for Neurodegenerative Diseases we aim to successfully combat neuropsychiatric diseases and thus allow people to grow old healthily. It is our objective to research the molecular mechanisms of development in their interaction with environmental and genetic risk factors. By elucidating the complex interdependencies, we lay the foundations for the development of new therapies, diagnostic procedures and successful prevention strategies. Close cooperation with clinical partners enables us to translate scientific knowledge rapidly into practical medical application, thus benefitting the patients."

Prof. Dr. Wolfgang Wurst, Director of the Institute of Developmental Genetics at Helmholtz Zentrum München and Chair of Developmental Genetics at Technische Universität München, manages the activities undertaken for the German Centre for Neurodegenerative Diseases.
He coordinates the "European Conditional Mouse Mutagenesis Programme" (EUCOMM) and its successor, the EUCOMMtools project, as well as the Helmholtz Alliance "Mental Health in an Ageing Society", which investigates mechanisms of neurodegenerative diseases.

Astroglia Reprogrammed into Functional Neurons

"It's like climbing a mountain for the first time: We see the goal, the summit, and we can also imagine the path. However, the ascent is still full of surprises and difficulties. Similarly, our sights are set on stimulating glial cells to regenerate injured brain tissue."

A research group at Helmholtz Zentrum München has reached a significant milestone in developing a possible therapy for neurodegenerative diseases such as Alzheimer's or stroke. The scientists were able to reprogram astroglial cells to specifically generate two distinct subtypes of functional neurons.

Prof. Dr. Magdalena Götz
2010 Federal Cross of Merit with ribbon — **2008** Alzheimer Research Award of the Hans and Ilse Breuer Foundation — **2007** Hansen Family Prize — **2007** Gottfried Wilhelm Leibniz Prize of the German Research Foundation — **since 2004** Director of the Institute of Stem Cell Research at Helmholtz Zentrum München and chair of Physiological Genomics at Ludwig-Maximilians-Universität Munich — **until 2003** Scientist and research group leader at Max Planck Institutes in Göttingen and Munich — **2000** Habilitation — **until 1996** Postdoc in Tübingen, London and Harlow

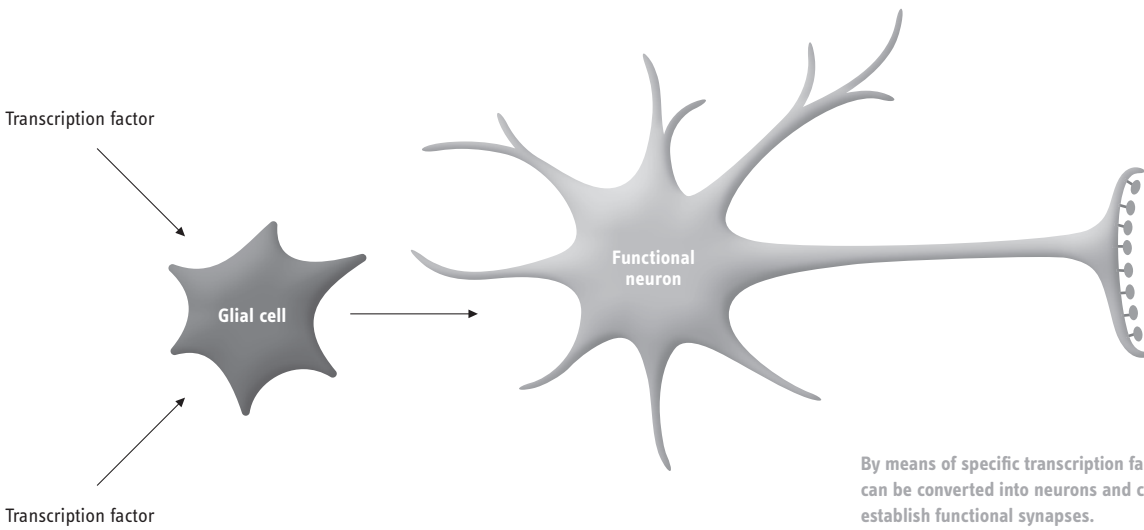
PD Dr. Benedikt Berninger
since 2005 Research associate at the Physiological Institute of Ludwig-Maximilians-Universität Munich and (since 2004) at the Institute of Stem Cell Research at Helmholtz Zentrum München — **until the end of 2003** Research associate at the Max Planck Institute of Neurobiology, Munich — **until 2000** Postdoc at the University of California, San Diego, USA

Cooperation Partners / Authors
Helmholtz Zentrum München Pratibha Tripathi, Timm Schroeder — **Helmholtz Zentrum München and Ludwig-Maximilians-Universität Munich** Christophe Heinrich, Sergio Gascón, Magdalena Götz, Benedikt Berninger — **Ludwig-Maximilians-Universität Munich** Robert Blum, Giacomo Masserdotti, Rodrigo Sánchez, Steffen Tiedt — **Center for Integrated Protein Science Munich (CIPSM)** Magdalena Götz

In a study based on a mouse model, the research team led by Magdalena Götz investigated whether and how astroglial cells can be specifically reprogrammed into functional neurons of the cerebral cortex. The researchers succeeded in transferring the genes encoding the transcription factors – these are proteins, which selectively regulate the transcription of the DNA – into the cells. The transcription factor Neurog2 stimulated the generation of excitatory neurons, while the transcription factor Dlx2 mediated the conversion of the astroglial cells into inhibitory neurons. Neurons are the cells in the brain that transfer information, whereas the star-shaped glial cells, so-called astroglia, serve as a scaffold and are involved in the metabolism of the brain. Astroglia are closely related to radial glial cells, which during embryonic development function in the forebrain as precursors for most neurons. Some glial cells in specific regions of the brain retain the ability to generate neurons in the adult brain as well.

It is still not known exactly how normal astroglial cells differ from radial glial cells with neurogenic potential. Scientists had previously already found that astroglia from the cerebral cortex of young mice – these are normally not able to generate neurons – can be stimulated to differentiate into neurons by inserting specific regulatory proteins.

Conversion of Astroglia into Neurons



By means of specific transcription factors brain astroglia can be converted into neurons and can be stimulated to establish functional synapses.

Now in the mouse model, the researchers succeeded in reprogramming the newly created neurons to the extent that they even establish functional synapses and – depending on the transcription factor used – generate either excitatory or inhibitory transmitter substances. This process could also be induced if astroglia from the adult brain had previously been reactivated by tissue injury.

These results nourish the hope that the barrier separating the closely related astroglia and the functional neurons can be overcome, enabling the development of future therapies that alleviate – or perhaps even cure – neurodegenerative diseases such as stroke or Alzheimer's.

The brain consists of two main types of cells: (1) neurons, which transmit information and (2) glial cells, which have a support function and are involved in the metabolism of the brain. In many degenerative diseases of the brain – stroke, Alzheimer's, Parkinson's – it is primarily the neurons that are damaged.

Original Publication

Christophe Heinrich et al.: Directing astroglia from the cerebral cortex into subtype specific functional neurons. PLoS Biol 8(2010) e1000373 | doi:10.1371/journal.pbio.1000373

Pax6 Regulates Survival of Specific Neurons

"Our research provides first evidence for why specific neurons in the adult brain survive for a long time. This is another piece of the mosaic that will help us understand the underlying mechanisms regulating the generation and survival of neurons. Using this knowledge, we hope one day to be able to replace dead neurons."

Dr. Jovica Ninkovic
2010 Scopus Neuroscience Award — **since 2007** Scientist at the Institute of Stem Cell Research, Helmholtz Zentrum München — **2005–2007** Postdoc, Institute of Stem Cell Research

Prof. Dr. Magdalena Götz
2010 Federal Cross of Merit with ribbon — **2008** Alzheimer Research Award of the Hans and Ilse Breuer Foundation — **2007** Hansen Family Prize — **2007** Gottfried Wilhelm Leibniz Prize of the German Research Foundation — **since 2004** Director of the Institute of Stem Cell Research at Helmholtz Zentrum München and chair of Physiological Genomics at Ludwig-Maximilians-Universität Munich — **until 2003** Scientist and research group leader at Max Planck Institutes in Göttingen and Munich — **2000** Habilitation — **until 1996** Postdoc in Tübingen, London and Harlow

Dr. Jack Favor
since 1987 Group leader of the research group Phenogenetics, Institute of Human Genetics, Helmholtz Zentrum München — **1979–1987** Research associate, Institute of Mammalian Genetics, at what is today Helmholtz Zentrum München — **1975–1979** Postdoc at the Georgia Institute of Technology, Atlanta — **1970–1976** Doctoral studies at the University of Rhode Island, Kingston / The Jackson Laboratory, Bar Harbor, PhD

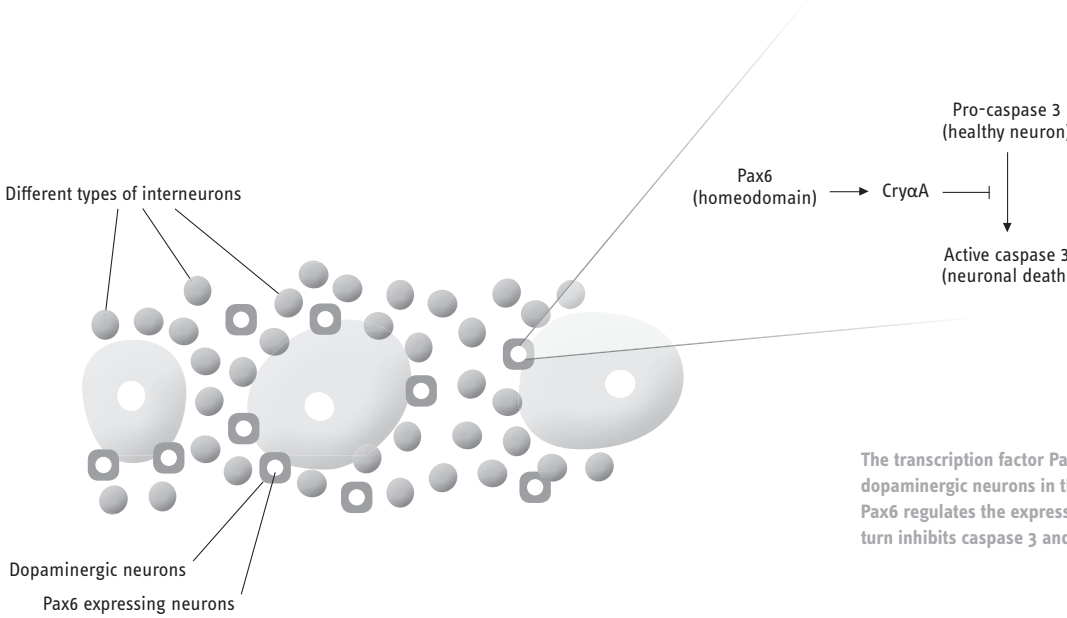
Cooperation Partners / Authors
Helmholtz Zentrum München Stefania Petricca, Timm Schroeder, Jack Favor, Luisa Pinto, Michael A. Rieger — **Helmholtz Zentrum München and Ludwig-Maximilians-Universität Munich** Jovica Ninkovic — **Helmholtz Zentrum München, Ludwig-Maximilians-Universität Munich and Munich Center for Integrated Protein Science CiPSM** Magdalena Götz — **Ludwig-Maximilians-Universität Munich** Alexandra Lepier — **Albert-Einstein-Medical-College, Bronx, New York** Jian Sun, Ales Cvekl

The transcription factor Pax6 was previously best known for its role in the development of the sensory organs. However, as scientists have now discovered, it also has an important function in the mature mammalian brain: It regulates the expression of a particular protein and thus ensures the survival of specific neurons. The discovery will help scientists better understand diseases such as Parkinson's or Alzheimer's and may represent an important contribution leading to new regenerative therapies.

Neurons in the brain must survive for the entire life of an individual, because in most regions of the brain they are no longer generated anew. If neurons die there – as is the case for example in neurodegenerative diseases – often only specific neurons are affected. However, it is not yet fully understood how this survival of neuronal subtypes is regulated. The research team of Magdalena Götz, Jovica Ninkovic and Jack Favor at Helmholtz Zentrum München and Ludwig-Maximilians-Universität Munich has identified a new signaling pathway regulating the survival of these neurons. What is decisive here is the transcription factor Pax6, which is primarily involved in embryonic development. However, in specific neurons – including the dopaminergic neurons in the olfactory bulb – it is also present in adult mammals. Until now, however, the utility and physiological role of this late expression remained elusive.

In their studies on the mouse model, Magdalena Götz and her team were able to elucidate the association between Pax6 and neuronal survival: Without Pax6 in the dopaminergic neurons of the olfactory bulb, a significant reduction of these neurons occurs within three months. Pax6 ensures the survival of the neurons by regulating the expression of crystallin αA. Previously, scientists had only studied this protein in the eye. Now for the first time it was shown to be present and have a function outside of the lens: In the neurons of the brain, crystallin αA inhibits the enzyme caspase 3 and thus prevents apoptosis.

Survival of the Dopaminergic Neurons in the Olfactory Bulb



The transcription factor Pax6 ensures the survival of dopaminergic neurons in the olfactory bulb of the forebrain. Pax6 regulates the expression of crystallin αA, which in turn inhibits caspase 3 and thus apoptosis.

The finding that this regulatory mechanism only applies to a specific neuron subtype is particularly important. Since only few neuron types in the adult brain express Pax6 the scientists are now investigating whether Pax6 can prevent apoptosis here as well. In any case, the results of the Munich scientists provide valuable basic knowledge to better understand the underlying mechanisms of diseases characterized by the loss of neurons. These include, for example, Alzheimer's and Parkinson's disease. The researchers hope that in the long run, their findings will lead to new approaches to prevention and regenerative therapy.

Parkinson's disease (PD) is primarily characterized by the death of the dopamine-producing neurons in the substantia nigra. Typical symptoms include slowed movement, hand tremor, rigid facial expression, stooped posture and a shuffling, small-step gait. Alzheimer's disease (AD) is characterized by a progressive deterioration of cognitive performance. Plaques and fibrillar deposits develop in the brain of patients, and neuronal death increasingly leads to a decrease in brain mass.

Original Publication
Jovica Ninkovic et al.: The Transcription factor Pax6 regulates survival of dopaminergic olfactory bulb neurons via christallin αA.
Neuron 68 (2010) 682-694 | doi:10.1016/j.neuron.2010.09.030

A Key Protein for Genetically Caused Parkinson's Disease

"By identifying genetic and environmental risks for Parkinson's disease and analyzing their systemic consequences in nerve cells, we want to obtain a better understanding of the molecular causes of this fatal disease. Through cooperative projects and translation of our findings into clinical applications, we seek to develop diagnostically relevant markers and effective therapeutic approaches to the treatment and cure of Parkinson's disease."

Genetic risk factors and mutations are increasingly identified as causes for the development of Parkinson's disease. Most of these mutations are located in the gene for leucine-rich repeat kinase2 (LRRK2). The gene encodes a protein kinase of still unknown physiological function. An international team led by Marius Ueffing at Helmholtz Zentrum München and the University of Tübingen has determined that the LRRK2 protein is of central importance for the integrity and dynamics of the cytoskeleton.

Prof. Dr. Marius Ueffing

since 2008 Director of the Research Institute for Ophthalmic Research, University Hospital Tübingen — **since 2010** Professor of Experimental Ophthalmology, University of Tübingen — **since 2008** Head of the independent Research Unit Protein Analytics of Helmholtz Zentrum München — **until 2007** Group leader at the Institute of Human Genetics, GSF-National Research Center for Environment and Health — **until 2000** Group leader in the Department of Medical Genetics, Ludwig-Maximilians-Universität Munich — **until 1997** Junior scientist and research group leader at the Institute of Clinical Molecular Biology and Tumor Genetics, GSF-National Research Center for Environment and Health — **until 1993** Scientist and laboratory head at Gödecke-Parke Davis, Freiburg — **1988–1991** Research associate, Columbia University, New York, PhD

Cooperation Partners / Authors

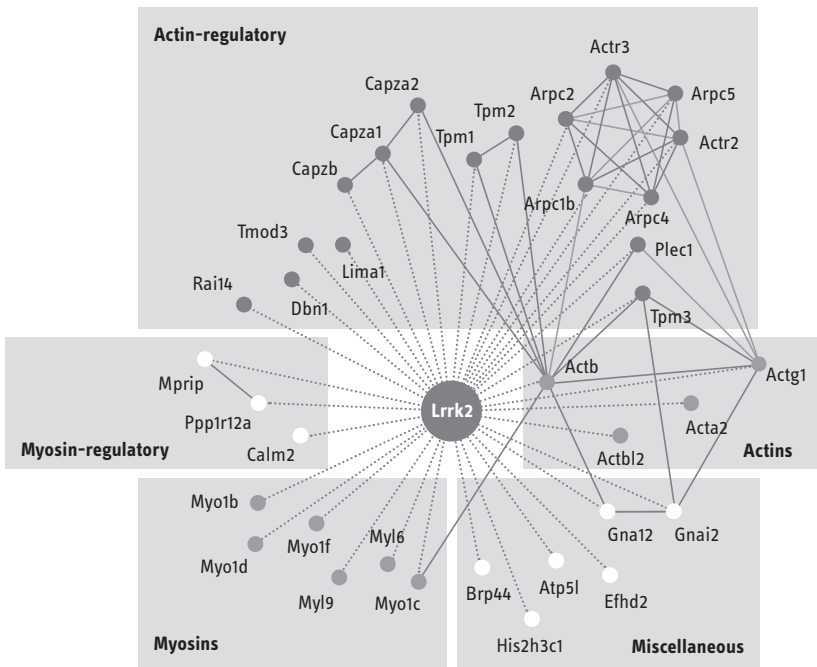
Helmholtz Zentrum München and Technische Universität München: Andrea Meixner — **Helmholtz Zentrum München** Karsten Boldt, Christian J. Gloeckner, Matthias Bauer, Norbert Kinkl, Marius Ueffing — **University of Tübingen** Karsten Boldt, Christian J. Gloeckner, Matthias Bauer, Norbert Kinkl, Marius Ueffing — **Department of Medical Protein Research, VIB, Ghent, and Ghent University, Belgium** Marleen Van Troys, Christophe Ampe — **Harvard Medical School, Boston University, USA und Dana-Faber Cancer Institute, Boston, USA** Manor Askenazi, Jarrod A. Marto — **Hebrew University of Jerusalem, Jerusalem, Israel** Manor Askenazi

The LRRK2 protein consists of several domains. One of them, the kinase domain, can mediate signals by transferring phosphate groups to target proteins and thus contribute to the regulation of cellular processes. Part of the mutations of LRRK2 associated with Parkinson's presumably lead to enhanced kinase activity; in turn, others show no rise in kinase activity, but rather increase the risk of developing Parkinson's disease.

As the team showed, the biological function of LRRK2 appears to be linked to dynamic processes of the cytoskeleton. In examining the totality of proteins (proteome) and their interactions (interactome), the researchers found that the LRRK2 protein interacts with proteins that are involved in the organization, in the construction and remodeling and in the maintenance of actin filaments. Particularly striking was the interaction with various forms of actin, a major component of the cytoskeleton.

LRRK2 binds to newly formed F-actin and can modulate its assembly in vitro. The researchers demonstrated this both in the NIH3T3 fibroblast cell line and in nerve cells. If in living NIH3T3 cells the synthesis of LRRK2 protein is inhibited by knockdown, this leads to marked changes in the morphology of the cells. They become elongated and thinner and lose their typical fibroblast shape. In cultured dopaminergic neurons of the midbrain – i.e. the cell types that are affected in Parkinson's patients – a knockdown of LRRK2 leads to a shortening of their neurites.

The Lrrk2 Protein and Its Interaction Partners



Interaction partners of the Lrrk2 protein are involved in the organization of actin filaments. Particularly numerous interactions exist with different forms of actin, one of the main components of the cytoskeleton.

Currently, scientists are investigating to what extent the interaction of the LRRK2 protein with components of the cytoskeleton is significant for the neurodegenerative processes in Parkinson's disease. For instance, in a cross-institute research collaboration, they are attempting to elucidate the spatial structure of the LRRK2 protein. Furthermore, in a joint project of the Helmholtz Association with the pharmaceutical company Boehringer Ingelheim (Helmholtz Alliance for Mental Health in an Aging Society), new strategies for drug optimization and ultimately innovative therapeutic concepts for the treatment of Parkinson's disease are being developed.

The cytoskeleton is a complex network of proteins in the cytoplasm of eukaryotic cells. It consists of thin filaments that can dynamically expand and contract and are responsible for the shape and mechanical stability of the cell, for the active movements of the cell as a whole and for movements and transports inside the cell.

Original Publication

Andrea Meixner et al.: A QUICK screen for Lrrk2 interaction partners – leucine-rich repeat kinase 2 is involved in actin cytoskeleton dynamics.
Mol. Cell. Proteomics 2010 | doi:10.1074/mcp.M110.001172

Homeoprotein Protects against Parkinson's Disease

"There is still no cure for Parkinson's disease, and all available therapies are only symptomatic. Our findings justify great optimism regarding the development of new therapeutic approaches."

Dr. Nilima Prakash

since 2002 Leader of the team Neuronal Differentiation and Maintenance in the research group Molecular Neurogenetics at the Institute of Developmental Genetics, Helmholtz Zentrum München — **2001–2004** Research associate at the Max Planck Institute of Psychiatry, Munich — **1998–2001** Postdoc, Karolinska Institutet, Stockholm / Sweden, and Weizmann Institute of Science, Rehovot / Israel — **1998** PhD, Institute of Cell Biochemistry and Clinical Neurobiology, University of Hamburg — **1987–1993** Undergraduate studies in Biology, University of Konstanz and King's College London, UK

Prof. Dr. Wolfgang Wurst

since 2002 Director, Institute of Developmental Genetics at the Helmholtz Zentrum München and chair of Developmental Genetics at Technische Universität München — **since 1997** Group leader of the research group Molecular Neurogenetics at the Max Planck Institute of Psychiatry, Munich — **1994–1997** Junior group leader, GSF – National Research Center for Environment and Health, Neuherberg, Institute of Mammalian Genetics — **1991–1994** Research associate at Samuel Lunenfeld Research Institute, Toronto, Canada — **1989–1991** Postdoc, Samuel Lunenfeld Research Institute of the Mount Sinai Hospital, Division of Molecular and Developmental Biology, Toronto, Canada — **1988–1989** Postdoc, University of Göttingen, Department of Immunogenetics — **1983–1988** PhD, Max Planck Institute of Immunobiology, Freiburg, and University of Göttingen

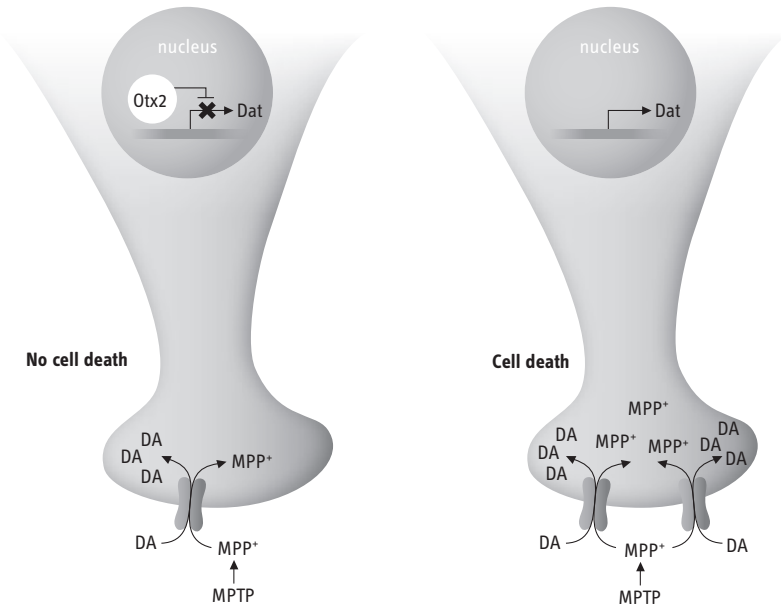
Cooperation Partners / Authors

Helmholtz Zentrum München Wolfgang Wurst, Nilima Prakash — **CEINGE Biotecnologie Avanzate / Institute of Genetics and Biophysics "A. Buzzati-Traverso", CNR, Naples** Michela Di Salvio, Luca Giovanni Di Giovannantonio, Daniela Omodei Dario Acampora, Antonio Simeone — **Università degli Studi del Sannio Benevento, Italy** Raffaele Prosperi

The homeoprotein Otx2 ensures the proper development of dopamine-producing neurons in the midbrain. The loss of these neurons plays an important role in Parkinson's disease. Otx2 also protects against the neurodegenerative effect of a neurotoxin that triggers an irreversible parkinsonism, as demonstrated by a German-Italian research team in a mouse model analyzed at the Helmholtz Center Munich.

The researchers of the Institute of Developmental Genetics led by Wolfgang Wurst demonstrated in a mouse model that the homeoprotein Otx2 protects against Parkinson's disease. Otx2 regulates neuron subtype identity in a specific region of the midbrain, the ventral tegmental area (VTA). Otx2 restricts the number of VTA neurons with efficient dopamine uptake via the dopamine transporter.In another region of the midbrain, the substantia nigra, Otx2 is basically absent, so that these neurons have a very efficient dopamine uptake. Dopamine is a very reactive molecule and is therefore harmful in large quantities. In the midbrain, Otx2 thus creates a balance between neurons with a low content of dopamine and those with a high content.

Neuroprotective Effect of the Otx2 Protein



The homeoprotein Otx2 protects neurons against premature cell death by limiting the uptake of the neurotoxin MPTP and / or of excessive dopamine (DA) via the dopamine transporter (Dat) into these cells. Otx2 inhibits the expression of the Dat gene in the cell nucleus. In the absence of Otx2, Dat protein synthesis is uninhibited. The neurotoxin MPTP is first metabolized outside of the nerve cells into its active form MPP+. MPP+ is selectively taken up via the dopamine transporter into the nerve cells, where it leads to neuronal cell death.

A disruption of this balance leads to an excess of harmful dopamine in the substantia nigra. These cells die, and a severe medical condition develops – Parkinson's disease. Heroin addicts sometimes display Parkinsonian symptoms that are due to contamination of the heroin with the neurotoxin MPTP. After MPTP intake, one of its metabolites is actively taken up by the neurons and accumulates in the substantia nigra and destroys these cells. Otx2 restricts the uptake of dopamine and / or MPTP and thus protects the neurons from cell death. The researchers therefore activated Otx2 in the neurons of the substantia nigra – thus achieving higher resistance of the cells against MPTP.

At present, shaking palsy is still a severe, incurable disease. To date, the neuronal loss in the substantia nigra cannot be stopped. Current therapies only alleviate the symptoms.

Dopamine is a chemical substance that mediates the transfer of information in the nervous system. In high concentrations, dopamine promotes neuronal death. MPTP (1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine), a contaminant of heroin, has the same effect and can therefore trigger Parkinson-like symptoms in drug addicts.

Original Publication
Michela Di Salvio et al.: Otx2 controls neuron subtype identity in ventral tegmental area and antagonizes vulnerability to MPTP.
Nature Neuroscience 13 (2010)1481-1488 | doi:10.1038/nn2661

Diagnosis

More Mathematics for Improved Radiation Protection in Radiodiagnostics

From Research to Successful Application

1960
To protect patients and medical personnel, the Neuherberg research center launches systematic radiation protection training

1964
The Institute of Radiation Protection begins systematically quantifying the amount of radiation exposure in x-ray examinations

1982
With the mathematical phantoms ADAM and EVA the Center develops the basis for dosimetry in radiodiagnostics

1985
The conversion factors for organ and skin doses determined at the Center are used in radiodiagnostics

1986
The Institute of Radiation Protection develops first voxel phantoms for medical and professional radiation protection

The Future

Better medical diagnostics through precise dosimetry and optimized image reconstruction

2009

New recommendations of the ICRP and the International Commission on Radiation Units and Measurements (ICRU) for calculating the organ dose are based on voxel models developed at the Center

2003

The research group Medical Physics develops first methods for reducing the radiation dose in computed tomography

2007

Christoph Hoeschen is awarded the Behnken-Berger Prize for new methods of dose reduction

2005

GOLEM is recommended by the International Commission on Radiological Protection (ICRP) for the development of a reference phantom

2006

Method of dose reduction in computed tomography and x-rays is patented

2001

The Institute of Radiation Protection presents the voxel phantom GOLEM

1895
The German physicist Wilhelm Conrad Röntgen discovers the x-ray.

1917
The Austrian mathematician Johann Radon hypothesizes and proves the Radon transform. The algorithm is the basis of today's computed tomography (CT).

1979
The British electrical engineer Sir Godfrey Hounsfield and the South African-born U.S. physicist Allan McLeod Cormack receive the Nobel Prize in Medicine for the development of computed tomography.

2004 ——

New algorithms and imaging geometries to reduce the radiation dose in radiodiagnostic procedures are subjected to first practice tests.

—— Future Vision

Improved devices provide high-quality images with a lower radiation exposure for the individual patient.

Better X-ray Images, Lower Doses

The former research group Medical Physics in the Institute of Radiation Protection, now the Research Unit Medical Radiation Physics and Diagnostics, began to develop dose-reducing methods in computed tomography in 2004. Through new techniques for optimized image reconstruction in computed tomography (CT) scans, the efficient adjustment of the radiation dose to each individual and through the development of new contrast mechanisms, the Center is helping to advance medical imaging towards a more personalized medicine.

Computed tomography (CT) is one of the most important imaging methods of modern medicine, but for the patient it involves relatively high radiation exposure. The Research Unit Medical Radiation Physics and Diagnostics, the successor to the former research group Medical Physics in the Institute of Radiation Protection, began developing algorithms to reduce exposure in 2004 led by Prof. Dr. Christoph Hoeschen. For the reconstruction of images from computed tomography data, his team, together with colleagues of the University of Oregon, developed a novel algorithm (orthogonal polynomial expansion on the disk, OPED) that makes better use of the information contained in the raw data. The technique was patented in 2006. OPED calculates the image data from the raw data of a CT scan without data manipulation steps as they are normally required. OPED is based on the fact that a function that describes an object can be approximately expressed by a polynomial. Through intelligent selection of the necessary basic functions, the experts can reconstruct a very accurate approximation of the actual properties of the object from the raw data of a CT scan, and this can be done easily and with relatively little computational effort.

About 60 percent of the population's medical radiation exposure comes from CT examinations.

In computed tomography, images are produced of cross-sectional "slices" of the body. When they are assembled they provide the physician with an accurate image of the interior of the body. About 60 percent of the population's medical radiation exposure comes from CT examinations – a growing trend in terms of the number of images produced and the associated radiation exposure.

While in computed tomography x-rays are used to produce images, the nuclear medicine procedures positron emission tomography (PET) and single photon emission computed tomography (SPECT) are based on the visualization of the distribution of a weak radioactively marked substance (radiotracer) in the organism. Nuclear medicine procedures serve primarily to represent functional processes in the body. By contrast, radiological procedures such as computed tomography visualize the anatomy of a patient.

The new reconstruction method can reduce the radiation exposure due to the CT scan by up to 50 percent. In voxel models developed at the Center which serve as ICRP reference individuals for dose estimates, raw data are simulated like those that a real CT scan would deliver. Quantitative evaluations show that the new method at half dose has at least the same signal-to-noise ratio as with conventional methods at full dose.

The next step leading to a further dose reduction was the development of new imaging geometries. In 2007 and in 2009, researchers from the Center presented optimized CT geometries. The new techniques enable the CT data to be captured much more precisely and in accordance with the theoretical requirements of the reconstruction technique. In the first approach, a detector and shield ring fixed in relation to the patient and are built into the diagnostic device in addition to the existing detectors. The researchers have presented a first demonstration model. As a further development, a device is currently being built that does not require a fixed detector but provides the same data geometry. The second approach is based on an open CT geometry, which offers variable resolution of the images and imaging geometries with parallel beams. This approach, too, was developed as a prototype for small animal imaging. A commercialization of this approach is being prepared together with an industrial partner.

Also in 2007, the research group presented a new approach for minimizing radiation doses in pediatric radiology: For chest radiographs in preterm infants, the system settings are optimized for the imaging conditions in order to arrive at the lowest possible radiation doses at the same high image quality.

From 2008 to 2010 Helmholtz Zentrum München also coordinated the EU-funded project MADEIRA (Minimizing activity and dose with enhanced image quality by radiopharmaceutical application), which seeks to reduce radiation doses in nuclear medicine. Within the framework of this project, a new method for reconstructing data in nuclear medicine imaging was developed, and a patent application was submitted in 2010. Furthermore, the OPED algorithm originally developed for the reconstruction of CT images is being adapted to the nuclear medicine application Single Photon Emission Computed Tomography (SPECT). SPECT images show the distribution of a radiopharmaceutical in the body. Depending on the kind of radiopharmaceutical, a kind of radioactively marked contrast medium, SPECT images can be used to assess the function of different organs. The image data of each individual patient are incorporated with other laboratory data into a biokinetic model, which can then be used for optimized imaging of the individual patient but with the lowest possible radiation exposure. Another advantage is that this model also offers the potential of personalizing and adapting nuclear medicine treatment to each individual patient.

Through the optimization of medical imaging techniques, the Center is helping to improve the benefit-risk ratio in favor of the patient and to increase success rates in therapeutic processes as e.g. radiation therapy through personalized analyses. Moreover, the Center is creating the basis for personalized treatment approaches by combining imaging with genetic and metabolomic screens of the tumors.

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"Through more efficient use of ionizing radiation in medical diagnostics and therapy, we are helping to optimize medical radiation applications and thus promote personalized medicine."

Prof. (NRNUM) Dr. Christoph Hoeschen —

is head of the Research Unit Medical Radiation Physics and Diagnostics which focuses on the development of methods and dose reduction in medical diagnostics and therapy.

1941
Regulation to protect against damage from x-rays and radioactive substances in non-medical facilities (x-ray Ordinance) becomes effective.

1957
With the establishment of the European Atomic Energy Community (EURATOM), basic standards for radiation protection in the workplace are adopted.

1995
The amendment to the Radiation Protection Ordinance widens the circle of occupationally exposed persons and sets new dose limits.

1982 —

Radiation doses in medical diagnostics are calculated on the basis of mathematical models.

— Future Vision

Individualized phantoms help to optimize medical radiation exposure.

Phantoms Improve Medical Radiation Protection

To protect the health of patients and occupationally exposed individuals, the Research Unit Medical Radiation Physics and Diagnostics at the Center develops computational models to precisely determine human radiation exposure. The mathematical phantoms ADAM and EVA have provided an important basis for dose determination in x-ray diagnostics since 1982. Models that were developed later on the basis of CT data were taken over as reference computational phantoms in 2009 by the International Commission on Radiological Protection (ICRP) and the International Commission on Radiation Units and Measurements (ICRU). They thus form the international basis for the establishment of guidelines for radiation protection.

Ionizing radiation, which individuals are exposed to in a work setting or in medical applications, cannot be determined directly in the body. The dose – a measure of the biological effect – is instead calculated from measured physical quantities as well as numerous conversion factors and model assumptions. An important role is played by the so-called phantoms. These computational models simulate the anatomy of the human body and render the dimensions and mass values of tissues and organs in detail, so that organ doses can be calculated from this data.

Scientists at the Institute of Radiation Protection developed the mathematical phantoms ADAM and EVA in 1982.

Various phantoms have been developed at the Institute of Radiation Protection at Helmholtz Zentrum München. These are used nationally and internationally for calculations within the framework of dose limit recommendations and for calculating organ and whole-body doses in occupational radiation protection and medicine.

Scientists at the Institute of Radiation Protection developed the mathematical phantoms ADAM and EVA in 1982. Here the anatomy is defined in position and size by mathematical relationships. In 1985, using these phantoms, conversion factors were determined for organ and skin doses for technical examination parameter settings as recommended in Germany for x-ray diagnostics. These conversion factors are still in use today.

Since the mid-1980s scientists at the Center have been developing voxel phantoms constructed from medical image data. These three-dimensional computational models, which are based on the real anatomy of an individual, are generally derived from the data of computed tomography or magnetic resonance imaging by segmentation of individual organs. They consist of numerous volume elements (voxels) and currently provide the most accurate representation of the human anatomy.

Worldwide there are various voxel phantoms in existence, many of which were developed at the Center. These phantoms are used in applications ranging from patient dosimetry in x-ray diagnostics and nuclear medicine to occupational radiation protection, but are also used for legislation. To set limits and calculate maximum permissible annual doses in the radiation protection legislation, "reference persons" are used. Exemplary of different age groups, body size and gender, organ and body doses from internal and external exposure can thus be determined. Here lawmakers base their legislation on the recommendations of national and international commissions, which update these at regular intervals according to the state of the science. The reference models used by the legislators are also derived from the recommendations of expert commissions.

In 2001 the Institute of Radiation Protection at the Center presented the voxel phantom GOLEM. In its dimensions it corresponds closely to the adult Reference Male according to the specifications of the International Commission on Radiological Protection (ICRP) and therefore serves as a starting point for the development of a reference voxel phantom.

In 2009 the ICRP and the International Commission on Radiation Units and Measurements (ICRU) adopted the voxel models developed in Neuherberg as male and female reference phantoms in the amendment of the recommendations on organ dose calculations. Members of the model family developed in the Center thus form the international basis for establishing guidelines in radiation protection.

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In the formulation of basic standards for radiation protection, the European Atomic Energy Community (EURATOM) draws upon recommendations of the International Commission on Radiological Protection (ICRP). This body is composed of representatives of the national radiological societies. The International Commission on Radiation Units and Measurements (ICRU) determines the radiation dose quantities and units. In the Federal Republic of Germany the Atomic Energy Act regulates the use of ionizing radiation. It is a framework regulation. The practical application of radiation protection measures is regulated by the Radiation Protection Ordinance and the x-ray Ordinance.

"Computational models in radiation protection are becoming ever more precise in rendering the human anatomy and in adapting to actual individual conditions. Thus, health protection can be continually improved in adapting radiation protection dose limits. In the field of x-ray diagnostics the individualized phantoms can help in furthering personalized dosimetry in medicine."

Maria Zankl ——

is concerned with the development of computational models for radiation protection. The mathematician is the deputy director of the Research Unit Medical Radiation Physics and Diagnostics.

1865
The Austrian monk Gregor Mendel describes the basic principles of heredity.

1927
The American biologist Hermann Joseph Muller shows that mutations can be induced by x-rays and receives the 1946 Nobel Prize in Physiology and Medicine for this achievement.

1987
The American geneticist Mario Capecchi reports in the journal Cell on the creation of first knockout mouse and is awarded the Nobel Prize in Physiology and Medicine for this discovery in 2007.

1979 —

The Center develops an approach for phenotyping mouse models of genetic alterations in humans which today is used throughout the world.

— Future Vision

A better understanding of complex diseases contributes to new therapeutic approaches.

Global Standards for Disease Models

In the 1970s and 1980s, the Institute of Mammalian Genetics developed standardized tests in the mouse model to enable, for the human situation, an estimation of the genetic risk due to radiation. The results are incorporated in the recommendations of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) on radiation protection and in part are still valid today. The mouse models developed at that time serve as basis for the investigation of the genetics of major human diseases. Today, animal models and population studies give insight into the genes involved in the pathogenesis of important widespread diseases and ultimately on molecular targets for new drugs and therapies.

In studies using mice in the late 1960s, the Department of Genetics headed by Prof. Dr. Udo Ehling set out to investigate the frequency of genetic mutations induced by radiation and chemicals. The goal was to elucidate the mutation process and determine the human genetic risk of mutagens in the environment. In the following years, the Institute of Mammalian Genetics was established, and there basic insights were gained on the point in time and type of mutations induced by radiation and chemicals. Based on dominantly inherited cataracts of the mouse, the Institute in 1979 developed one of the first test procedures allowing direct comparison with human hereditary diseases. In 1985 this procedure was presented under the name "multiple endpoint approach" and was the first integrated approach to phenotyping mutant mice – an idea that was adopted 20 years later by the German Mouse Clinic. Today this concept of systemic phenotype analysis is recognized and applied worldwide.

Beginning in the late 1980s, new molecular biological methods enabled the investigation of the genetic causes of various diseases.

Beginning in the late 1980s, new molecular biological methods enabled the investigation of the genetic causes of various diseases. Under the direction of Prof. Dr. Rudi Balling the Institute of Mammalian Genetics began to develop animal models for human diseases. At first, experimental embryological and cell biological methods were used to elucidate the molecular mechanisms which regulate embryonic organ development. The large-scale screen under the auspices of the German Human Genome Project sought to systematically elucidate the function of the genes in em-

bryonic development as well as in the development of disease. With the further development of gene trap technology and the establishment of the ENU mutagenesis screen at Neuherberg, national and international projects were given important impulses for the functional elucidation of the human genome.

In 2000 a new institute evolved out of the Institute of Mammalian Genetics: the Institute of Experimental Genetics with Prof. Dr. Martin Hrabě de Angelis as director. Here the German Mouse Clinic (GMC) was established and built up under the auspices of the National Genome Research Network. At the GMC, mutant mouse lines are phenotyped under standardized conditions. Together with German and international partners, more than 200 mouse models have been phenotyped here for genetically caused diseases. A main focus of the German Mouse Clinic is on metabolic diseases such as diabetes mellitus.

The other important institute that emerged from the Institute of Mammalian Genetics in 2002, namely the Institute of Developmental Genetics headed by Prof. Dr. Wolfgang Wurst, is concerned with the functional analysis of genes that are involved in the development of the nervous system. The Institute focuses on the underlying mechanisms of common neurological diseases such as Parkinson's and Alzheimer's disease as well as genetic eye diseases. It coordinates the European part of the world's largest research project aiming at the mutation of all protein coding genes in embryonic mouse stem cells to eventually elucidate their function and their role in pathogenesis.

The identification and functional characterization of human disease genes are the focus of the Institute of Human Genetics, which was founded in 2000 and is headed by Prof. Dr. Thomas Meitinger. Here large-scale population studies provide a database which can be used to identify corresponding gene variants. Over the long term, the identified variants shall serve as molecular targets for new drugs and therapies.

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Mice are ideal model organisms for the elucidation of gene functions. They multiply rapidly; the mouse genome containing approximately 22 000 genes is almost completely deciphered, and it is largely consistent with the genetic material of humans. Many human and mouse genes correspond and can trigger the same diseases in mouse and man. One of the first mouse models studied at the GMC was the mutant "Beethoven", a mouse line that with increasing age suffers from hearing loss.

In gene trap mutagenesis a reporter gene is randomly integrated into the genome of the cell; the mutated gene can be easily identified by the reporter gene.

N-Ethyl-N-nitrosourea, also known as ENU, is a strong carcinogen and highly potent mutagen that can induce point mutations as they occur in nature.

In the Multiple Endpoint Approach the influence of a mutation on the entire organism is studied.

"Together with our international partners, we are building a library of conditional mutant mouse embryonic stem cells. This resource enables the international scientific community to systematically investigate the function of all genes during development and in the adult mouse. Thus, disease processes can be elucidated, and genes can be studied in their context. This gene function analysis will shed light on the pathogenesis of important widespread diseases such as Alzheimer's disease, depression, diabetes mellitus or chronic lung diseases."

Dr. Cornelia Kaloff —

Institute of Developmental Genetics, is the manager of the European projects EUCOMM and EUCOMMTOOLS which develop mouse models of human genetic diseases using new approaches.

"Seen from an international perspective, the mouse will remain also in the future the most important model organism for studying and understanding the underlying molecular mechanisms of genetic diseases. The German Mouse Clinic makes a major contribution to the development of diagnostic and treatment options for genetically related diseases. Its systemic analysis, comprehensive and standardized data collection and its use of state-of-the-art technologies form the basis for the success of the German Mouse Clinic."

Dr. Valérie Gailus-Durner —

Institute of Experimental Genetics, is scientific-administrative director of the Geman Mouse Clinic, in which genetically caused diseases are analyzed using mouse models.

Dr. Dr. Melanie Königshoff
is looking for new therapies for severe chronic lung diseases. The scientist is conducting research at the Comprehensive Pneumology Center, which was founded by Helmholtz Zentrum München and three partners as a translational research center. In 2010 Melanie Königshoff was awarded a Starting Grant by the European Research Council. This will provide her with around 1.5 million euros during the next five years in order to research mechanisms of lung regeneration.

Director of the Graduate College "Lung Biology and Disease" and group leader of the junior research group at the Comprehensive Pneumology Center, Helmholtz Zentrum München — **until 2009** clinical training and postdoc at the lung center of the University of Gießen — **2009** Co-author of "Prüfungswissen Physikum" — **2007** Ph.D. in medicine at the University and the university hospital of Gießen — **2002** Author of the textbook "Biochemie" — Teaching position in biochemistry, pharmacology, pathobiochemistry, and medicine at the university hospital and the University of Gießen — **2004** Ph.D. in biochemistry at the University of Gießen — Medical degree at the University of Gießen — Born **1976** in Wilhelmshaven

2009 Young Scientist Delegate of the European Respiratory Society — Selected for "Capital" magazine's "Young Elite" (4 × 40 under 40 in the Science section) — **2006 and 2008** PneumoUpdate Award — **2006** Young Investigator Award of the International Colloquium of Lung Fibrosis — **2006** Cell and Molecular Biology Young Scientist Award of the European Respiratory Society

More Air for Diseased Lungs

Starting Grant from the European Research Council for Melanie Königshoff

“Being able to effectively treat lung diseases is a great challenge to medicine. We were able to identify biochemical signaling pathways that play a key role in repair mechanisms of lung tissue. We are looking for a therapeutic approach to regenerate diseased human lung tissue. I hope that in future our research will contribute to being able to offer therapies that improve the lung architecture.”

Lung Research

at Helmholtz Zentrum München since 1960

1964
Research into lung damage caused by radon

1968
Research into the absorption and distribution of particles in the lung as part of aerosol research

1983
Foundation of the interdisciplinary Munich Air Pollution Research Network (MAGL) in cooperation with both Munich universities

1984
First evaluation of the lung cancer risk caused by radon in homes

1985
Groundwork for recommendations on radon exposure in homes

1985
Development of the lung clearance model

1986
Launch of the "Inhalation Project"

1990
Research into symptoms of the respiratory system in children in an East-West comparison

1990
Erfurt partner location for US Particle Center in Rochester

1990
Foundation of the Institute of Epidemiology

1993
Foundation of the Institute of Inhalation Biology

1995
Particle deposition model for the respiratory tract becomes international standard

The Future

Many lung diseases still cannot be cured. Utilizing close links between basic research and clinical application, the Comprehensive Pneumology Center aims to develop efficient therapies and preventive strategies

2010
Helmholtz Zentrum München becomes a partner of the German Centre for Lung Research (DZL)

2009
The Institute of Inhalation Biology is transformed into the Institute of Lung Biology and Development

2007
Development of an inhaler for the application of asthma medication in children

2006
Clinical Cooperation Group "Inflammatory Lung Diseases" develops inhalative vaccination strategies

2005
Expansion of the KORA study center to include the effects of fine particles on the cardiovascular system

2005
Re-evaluation of the radon-induced health risk

2004
European studies on radon risk in homes presented

2004
Scientists of the Center act as advisors for the transposition of radon risk levels into precautionary levels

2003
First evidence of the effects of fine particles on myocardial infarction risk

2002
Inamed launches the AKITA inhalation system

2000
Networking competences in the project field "Relevance of Aerosols for Health"

2000
Results of the research into the East-West comparison are included in the recommendation of the US Environmental Protection Agency

2000
Cooperation with US-EPA for research into the effects of fine particles on health

1998
The Institute of Inhalation Biology sets up the spin-off Inamed GmbH

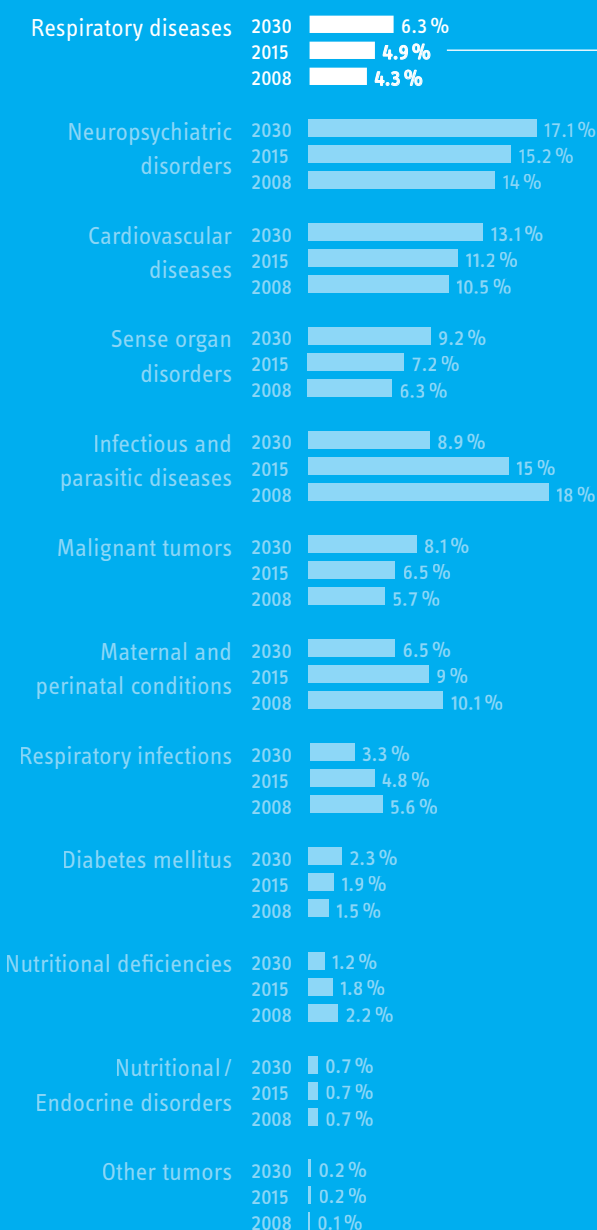
1998
Cooperation agreement with the American Environmental Protection Agency EPA

1990–1997
Research into the connection between radon in homes and lung cancer

Partner of the German Centre for Lung Research (DZL)

Helmholtz Zentrum München

Causes of the Global Burden of Disease: Lung Diseases Continue to Rise Sharply



	2008	2015	2030
Chronic obstructive pulmonary disease (COPD)	2.3 %	2.7 %	3.8 %
Asthma	1.1 %	1.2 %	1.4 %

These projections show the share of the overall burden of disease in percent, stated in DALYs.

One DALY (Disability Adjusted Life Year) is a year of healthy life lost to disability. The "DALY" figure aims to not just summarize the mortality, but also the impairment of the normal life, free of complaints, through an illness, by providing a comparable measure.

Source: Projections of mortality and burden of disease, world health organisation, baseline scenarios 2008, 2015, 2030
www.who.int/healthinfo/global_burden_disease/projections/en/index.html

From June 2011, **the German Centre for Lung Research (DZL)** will pool resources for researching lung diseases in Germany. The DZL is one of the six German Centres for Health Research currently being set up by the Federal Ministry of Education and Research as part of a nationwide competition. Helmholtz Zentrum München, together with Ludwig-Maximilians-Universität, the university hospital Munich and the Asklepios Pulmonary Hospital Gauting, is one of the five partner locations of this centre. The DZL, which involves a total of 18 universities, hospitals and research institutions, aims to contribute to a faster transfer of research results from the laboratory to broad medical care.

"As a location of the German Centre for Lung Research, we intend to successfully combat lung diseases. It is our objective to elucidate the causes of chronic lung diseases and to develop new therapies. In doing so we focus on chronic obstructive pulmonary disorder (COPD), asthma, lung cancer, and lung fibrosis, which are becoming increasingly common diseases. The translational 'Comprehensive Pneumology Center' (CPC) combines the required basic research and clinical research under one roof, thus ensuring that, through interdisciplinary cooperation, new knowledge reaches clinical practice rapidly, for the benefit of the patients."

Prof. Dr. Oliver Eickelberg coordinates the contributions of Helmholtz Zentrum München for the German Centre for Lung Research. Eickelberg is Director of the Institute of Lung Biology at Helmholtz Zentrum München, Chair of Experimental Pneumology at Ludwig-Maximilians-Universität Munich (LMU), and chairman of the Comprehensive Pneumology Center, which is jointly supported by Helmholtz Zentrum München, LMU, the university hospital Munich, and the Asklepios Pulmonary Hospital Gauting.

The Allergen Content of Birch Pollen Varies Widely

"The goal of our research is to determine the allergy influencing potency of our ambient air: To achieve this, we measure pollutants, bacteria, mold spores and of course airborne allergens, in order to attain better protection for allergy sufferers."

Depending on the stage of the ripening process, the allergen content of birch pollen fluctuates greatly. This was the outcome of a multiyear study at the Center of Allergy and Environment Munich (ZAUM), which is affiliated with Technische Universität München and Helmholtz Zentrum München. An integrated measurement approach taking into account not only the quantity but also the allergen potency of the pollen shall substantially improve the reliability of exposure predictions for allergy sufferers in the future.

Prof. Dr. Jeroen Buters

since 2007 Deputy director of the Center of Allergy and Environment Munich (ZAUM, Director Prof. Dr. Carsten Schmidt-Weber), Helmholtz Zentrum München and Technische Universität München — **since 2005** Registered toxicologist, German Society for Experimental and Clinical Pharmacology and Toxicology (DGPT) — **seit 2001** Group leader of the research group Toxicology and Exposure Research at the Center of Allergy and Environment (ZAUM) — **1997–2000** Habilitation at Technische Universität München — **1992–1996** Visiting fellow at the National Cancer Institute, National Institutes of Health in Bethesda, Maryland (USA) — **1989–1992** Postdoc at Hoffmann-LaRoche, Basel (Switzerland)

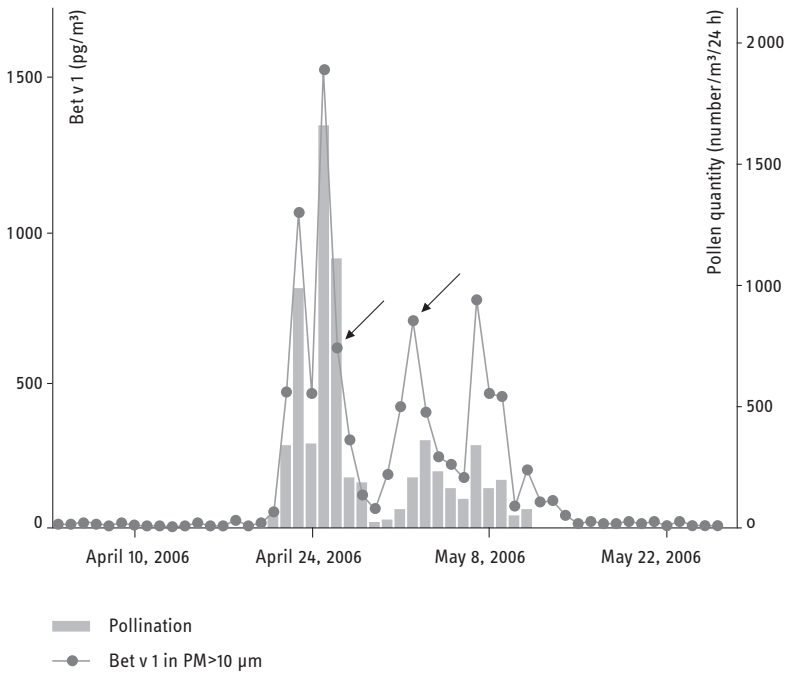
Cooperation Partners / Authors

Helmholtz Zentrum München and Technische Universität München Jeroen T. M. Buters, Heidrun Behrendt, Stefanie Ochs, Gudrun Pusch, Wolfgang Schober, Ingrid Weichenmeier — **Helmholtz Zentrum München** Wolfgang Kreyling — **National Institute for Public Health and the Environment, Centre for Environmental Health Research, Bilthoven (Netherlands)** A. John F. Boere

One in five northern Europeans develops an allergy in the course of his / her lifetime, usually to grasses or birch pollen. To predict the allergen burden of the ambient air, the quantity of pollen grains in the ambient air is routinely counted. With this approach it remains unclear to what extent the pollen count is a representative measure for allergen exposure in the ambient air. Now, Jeroen Buters of the Center of Allergy and Environment (ZAUM) can answer this more accurately. Using standard pollen traps, his team has measured pollen concentrations in the ambient air during the entire birch pollen season every year since 2004 and has correlated this pollen count with the respective weather data. Parallel to this, the quantity of the main allergen Bet v 1 was collected and extracted with a cascade impactor for three different particle sizes and was quantified using ELISA technology.

Qualitatively, the pollen counts and the allergen contents followed the same trends. Quantitatively, however, deviations were observed, some of which were considerable: For example, the pollen collected in 2007 contained double the amount of allergen as the pollen collected in 2004. Moreover, some of the samples collected on different days in the same year but containing equal amounts of pollen varied in their allergen content by as much as tenfold. In separate studies Buters and his colleagues were able to show that these differences correlate with the ripening process of the pollen: The riper they are when they are released by the birch catkins – which is dependent on the weather – the greater their allergen potential.

Daily Tracking of Birch Pollen and Their Allergen Content in Munich



Birch pollen samples taken from the same location but on different days show in part considerable differences in their allergen potency. This is particularly evident when comparing the two days marked by arrows: On April 26th the allergen content is almost equal (points), however, the pollen count (bar) is five times higher than on May 2nd.

Since 2009 Buters has been coordinating the European network HIALINE (Health Impacts of Airborne Allergen Information Network, www.hialine.eu), which measures airborne allergens. Thirteen partners from eleven countries are investigating the three most important wind-pollinated allergenic plants in Europe – birch trees, olive trees and grasses. First results confirm the differences in allergen potency, as was already shown in the Munich study on birch trees. The studies of the other kinds of pollen also demonstrate that pollen counts only reflect real allergen exposure in the ambient air to a certain extent. An integrated measurement approach, which includes the allergen content, shall clearly improve the reliability of exposure predictions for allergy sufferers and for the general population.

The protein Bet v 1 is produced by ripe birch pollen and is considered the main cause of birch pollen allergy. The airborne birch pollen comes into contact with the mucous membranes of the eyes, nose and throat, where it releases Bet v 1. In susceptible people the proteins trigger a specific immune response which is often accompanied by severe allergic symptoms such as bloodshot, watery eyes, sneezing and runny nose.

Original Publication
Jeroen T. M. Buters et. al.: The allergen Bet v 1 in fractions of ambient air deviates from birch pollen counts. Allergy 65 (2010) 850-858 | doi:10.1111/j.1398-9995.2009.02286.x

Improved Repair Processes of the Lung

"To date, we do not know whether or not human lung tissue can regenerate, and if yes, just how it does so. In the mouse model we could show that regeneration processes can be activated. I hope our research contributes to providing new therapies in the future which will improve the lung architecture."

Dr. Nikolaus Kneidinger
since 2010 Postdoc at the Excellence Cluster Cardio-Pulmonary System (ECCPS), Giessen — **2008–2010** Graduate program University of Giessen Lung Center; PhD at the University of Giessen Lung Center, Justus Liebig University Giessen and the Institute of Lung Biology and Disease, Helmholtz Zentrum München

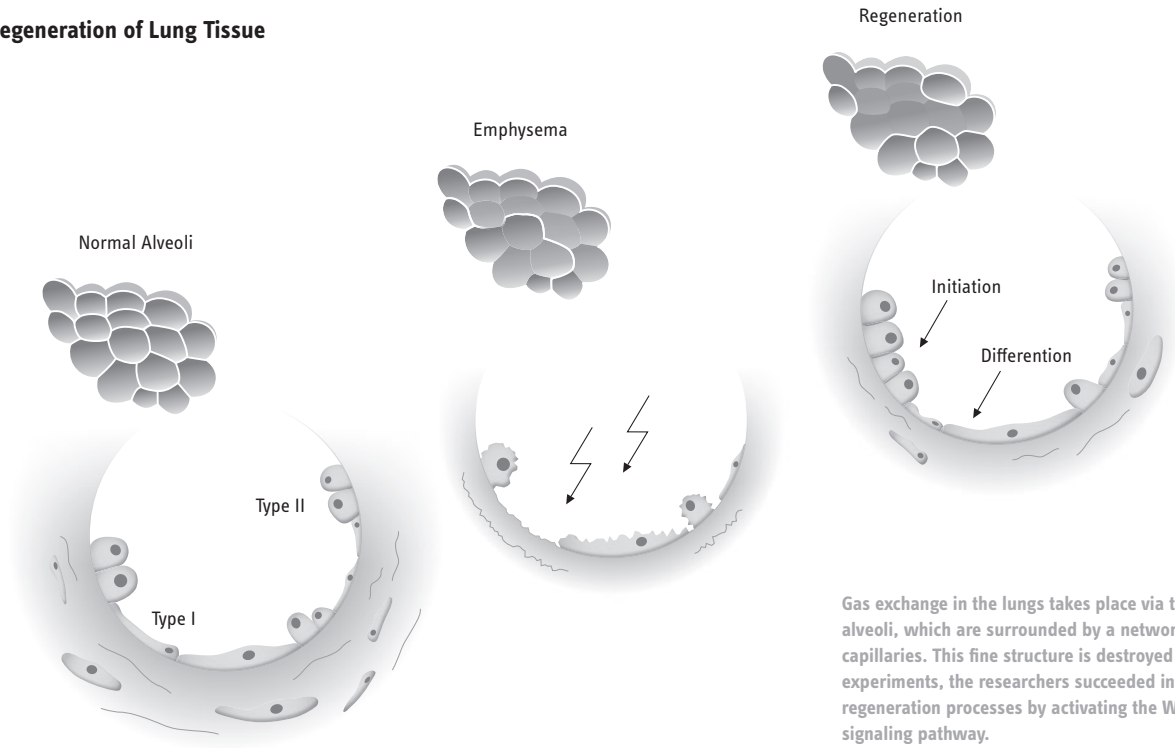
Dr. Dr. Melanie Königshoff
since 2010 Director of the Helmholtz Research School Lung Biology and Disease and junior group leader at the Comprehensive Pneumology Center, Helmholtz Zentrum München — **2007–2009** Postdoc at the Lung Center of the University of Giessen — **2004–2007** Resident doctor and doctoral studies (PhD), University and University Hospital Giessen

Cooperation Partners / Authors
University of Giessen Nikolaus Kneidinger, Rory E. Morty, Ralph Theo Schermuly, Rio Dumitrascu — **Helmholtz Zentrum München** Ali Önder Yildirim, Jens Callegari, Shinji Takenaka, Maria Magdalena Stein, Alexander Bohla, Oliver Eickelberg, Melanie Königshoff — **Ghent University Hospital** Ken R. Bracke, Guy G. Brusselle

The loss of lung tissue in patients with chronic obstructive pulmonary disease (COPD) may possibly be repairable. A research team of Helmholtz Zentrum München at the Comprehensive Pneumology Center was able to activate the WNT/β-catenin signaling pathway in the mouse model and thus achieve an improvement in the clinical picture. This is an important step towards the development of new therapies for humans.

COPD is the fourth leading cause of death worldwide – so far without any chance of a cure. As the disease progresses, the patients experience a loss of lung tissue and destruction of the lung architecture, also called emphysema. The capability of the lungs to exchange gases – so essential to life – is increasingly lost. The junior research group of Melanie Königshoff at the Comprehensive Pneumology Center, together with colleagues of the University of Giessen, showed a new approach to improving the repair processes of the lung. For their study the researchers used the WNT/β-catenin signaling pathway, which plays a crucial role in lung development. For the first time it was shown that this signaling pathway is also involved in the development and progression of COPD.

Regeneration of Lung Tissue



Gas exchange in the lungs takes place via the thin-walled alveoli, which are surrounded by a network of blood capillaries. This fine structure is destroyed in COPD. In their experiments, the researchers succeeded in restarting the regeneration processes by activating the WNT/β-catenin signaling pathway.

In tissue samples of COPD patients, the researchers found that the WNT/β-catenin-signaling pathway is inhibited in COPD. These findings were confirmed in various COPD and emphysema mouse models, and the mechanism was investigated more precisely. By activating the WNT/β-catenin signaling pathway, the team led by Melanie Königshoff succeeded in attenuating the development of an experimental emphysema and in regressing a pre-existing emphysema.

The findings of the study show that when the WNT/β-catenin signaling pathway is inhibited, lung tissue is destroyed and a repair does not take place. A reactivation of the signaling pathway thus represents a new approach to developing therapies for COPD patients.

Chronic obstructive pulmonary disease (COPD) is characterized by a reduction of the vital gas exchange surface; this change is also known as emphysema. Thirteen percent of the German population over 40 years suffers from COPD. The best known risk factors include cigarette smoke and polluted air. The exact mechanisms that lead to the disease are not known, and the disease cannot yet be cured.

Original Publication
Nikolaus Kneidinger et al.: Activation of the WNT/β-catenin pathway attenuates experimental emphysema. Am. J. Respir. Crit. Care Med. 2010: Epub Oct. 1 | doi:10.1164/rccm.200910-1560OC

Improved Cost-Utility Analysis of Treatments for Lung Patients

"We want to ensure that medical data are not the only parameters for evaluating an intervention. We need to focus more on the patients' health-related quality of life when making health economic assessments."

Dr. Petra Menn

since 2009 Research associate at the Institute of Health Economics and Health Care Management, Helmholtz Zentrum München — **2009** PhD, Ludwig-Maximilians-Universität Munich — **2006–2009** Doctoral student at Helmholtz Zentrum München

Cooperation Partners / Authors

Helmholtz Zentrum München Petra Menn, Rolf Holle — **Asklepios Pulmonary Hospital Gauting** Norbert Weber

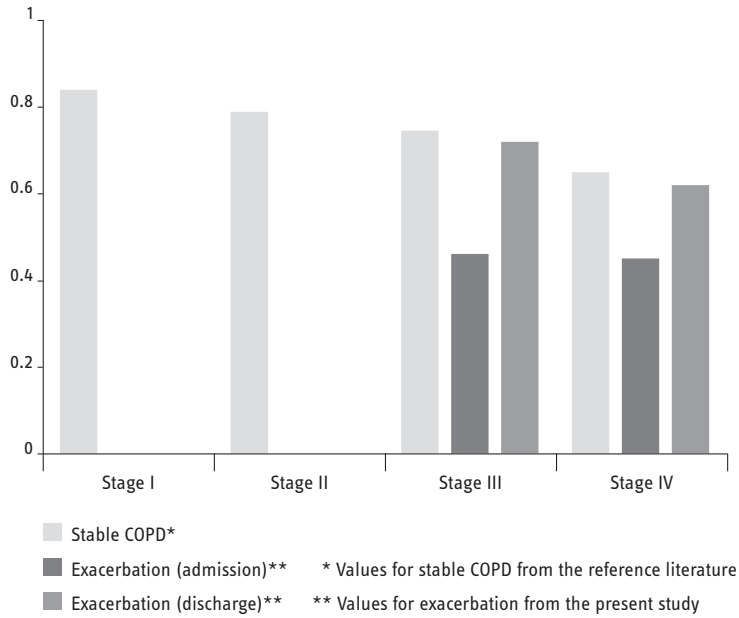
The quality of life of patients with chronic obstructive pulmonary disease (COPD) usually improves significantly after a hospital stay. This effect was now demonstrated for the first time using generic survey instruments that are suitable not only for a specific disease but rather for diseases in general.

In COPD patients, the progression of the disease often leads to an acute deterioration of the patients' condition, a so-called exacerbation, which often has to be treated in the hospital. The health status from the perspective of the patient can be measured using different methods. During stable disease phases the generic questionnaire forms EuroQol 5 Dimension (EQ-5D) and Short Form 12 (SF-12) are often used. However, to date, in the case of exacerbations only questionnaires have been used that are specific to lung diseases, such as St. George's Respiratory Questionnaire (SGRQ). This can make disease-specific statements, but no general statements about health status, a prerequisite for health economic assessments. This is especially true if the cost-effectiveness of therapies shall be compared and evaluated across multiple diseases.

Petra Menn at the Institute of Health Economics and Health Care Management at Helmholtz Zentrum München, together with colleagues from the Asklepios Pulmonary Hospital Gauting, studied ways to assess the health status of COPD patients during an acute exacerbation of disease. To this end, the scientists used the generic questionnaires EQ-5D and SF-12 and the disease-specific SGRQ.

In total, 117 patients with GOLD stages III and IV responded to the questionnaires upon admission and discharge from the hospital. GOLD Stage III means that the forced expiratory volume in one second (FEV1) is between 30 and 50 percent of the normal value. In stage IV the one-second volume is below 30 percent. According to GOLD (Global Initiative for Chronic Obstructive Lung Disease), COPD is divided into different stages ranging from I (mild) up to IV (very severe).

Quality of Life of COPD Patients with Severe Exacerbations



At the beginning of the exacerbation there is a clear deterioration in the quality of life in comparison to stable disease phases. By the time the patient is discharged, however, the values rise again approximately back to baseline levels.

The analysis of the data in all three questionnaires showed a significant increase in the quality of life of patients at discharge from the hospital. In the comparison of the three questionnaires, the SF-12 proved to be less practical because many patients answered the questions only incompletely. Therefore, a calculation of the index value for the quality of life was not possible. The SGRQ was particularly suited to distinguish between disease stages. However, this questionnaire is disease-specific and therefore cannot be used for health economic cost-utility analyses.

Using the generic questionnaire EQ-5D, the researchers could assess health status from the perspective of the patient, even beyond COPD-specific complaints. Although differences between the GOLD stages III and IV were less pronounced and only limited restrictions of the health status were recorded at discharge from the hospital, the EQ-5D was found to be a suitable generic instrument to measure the quality of life of COPD patients. Thus it can be used to assess the cost-utility of COPD therapies.

The impact of medical treatment on health-related quality of life can be measured using different methods. Disease-specific questionnaires are less suited for health-economic considerations, since the comparison of the cost-effectiveness of different therapies for different diseases is also interesting. That is why generic survey instruments suitable for various diseases are required.

Original Publication
Petra Menn et al.: Health-related quality of life in patients with severe COPD hospitalized for exacerbations – comparing EQ-5D, SF-12 and SGRQ. Health and Quality of Life Outcomes 8:39 (2010) | doi:10.1186/1477-7525-8-39

Prevention

Precise Calculation of Exposure to Cosmic Radiation on Flight Routes

From Research to Successful Application

1966
The Institute of Radiation Protection develops measurement and calculation methods for mixed radiation fields

1975
The Institute of Radiation Protection begins research on radiation exposure in aircraft

1991
In collaboration with the "Berufsgenossenschaft für Fahrzeughaltung" and the German Lufthansa, numerous test flights are carried out

1994
The Center is the first to provide homogeneous data records on the cosmic radiation exposure of flight crews

The Future

Better medical diagnostics through precise dose determination and optimized image reconstruction

2010

EPCARD.Net, the Internet version of the calculation software is approved

2007

Measurements taking solar flares into account begin at the research station on Spitzbergen

2005

Sensors for the continuous measurement of cosmic neutrons begin operation on the Zugspitze

2003

EPCARD is approved by the Federal Aviation Authority

1995

The Center begins with the development of the calculation model EPCARD

1854
The origin of epidemiology: During a cholera outbreak the British physician Dr. John Snow traces the source of the infection to contaminated water in a public well.

1980
The British biochemist Frederick Sanger receives the Nobel Prize in Chemistry together with the Americans Paul Berg and Walter Gilbert for the development of DNA sequencing.

1983
The U.S. biochemist Kary Mullis describes the polymerase chain reaction (PCR). He receives the 1993 Nobel Prize in Chemistry for his discovery of artificial DNA amplification.

2005 —

KORA data are the basis for new insights into diabetes and myocardial infarction.

— Future Vision

The Helmholtz cohort provides new insights into the prevention and treatment of diabetes and myocardial infarction.

Research Platform for the Health of the Population

Risks associated with an increasing number of major diseases can be more precisely defined through large-scale population-based studies. Epidemiological studies provide data on the incidence and distribution of diseases and the underlying genetic risks, lifestyle and environmental factors. A key basis of many international studies is the epidemiological research platform KORA, which has been built up and is coordinated by the Center.

Epidemiology studies diseases in human populations and the risks of their occurence. In 1985, the Institute of Medical Informatics and Systems Research headed by Prof. Dr. Wilhelm van Eimeren began in Augsburg with population-based research and established a registry of acute myocardial infarction. The project is part of the global cardiovascular MONICA study (Monitoring Trends and Determinants in Cardiovascular Disease) of the World Health Organization (WHO), which records morbidity and mortality of cardiovascular disease in defined study regions and correlates these to suspected risk factors.

Helmholtz Zentrum München has been investigating cardiovascular risk on the population level since 1985.

Through the standardized analysis of parameters in blood and urine and the invention of genotyping, the technical basis was laid for epidemiology to study disease risks on the molecular level as well. In 1996 the Augsburg MONICA project was followed by the newly founded research platform KORA (Cooperative Health Research in the Augsburg Region) coordinated by Prof. Dr. Dr. H.-Erich Wichmann. The KORA platform comprises a large population-based cohort with a total of more than 18 000 participants from the study region as well as the epidemiological myocardial infarction registry, which has been in continual operation since 1985. Thus, for more than 25 years Helmholtz Zentrum München has been studying cardiovascular risk on the population level.

All cohort participants are sent questionnaires in regular, several-year intervals asking them about their health status and health care. Some participants are re-examined. By participating, the residents of the Augsburg region make a significant

contribution to the knowledge base: The regular examinations and surveys enable scientists to describe the participants' health profile over a long period, in part over 20 years.

In the 1990s the KORA cohort made an important contribution to the elucidation of the role of inflammatory proteins in the development of atherosclerosis. The association between type 2 diabetes and increased risk of myocardial infarction was analyzed thoroughly in KORA. In 2004, in the course of a study on particulate matter, the scientists discovered a correlation between exposure to ultrafine particles in the ambient air and the occurrence of atherosclerosis and heart attack. In 2006 the population-based costs of obesity in adults were determined, and studies in 2009 showed that disease management programs could improve the treatment of type 2 diabetes in key areas.

In addition to cardiovascular diseases, the spectrum of the KORA survey has been significantly broadened. Today KORA includes studies on type 2 diabetes, metabolic syndrome, respiratory illnesses, allergies, mental disorders and healthy aging. The platform has a large biobank of blood, urine and cell samples and a broad database of life style factors, preclinical and clinical information, from which also genetic research has profited enormously in recent years. The linking with innovative biomedical methods and the translation of the results for effective prevention open up new avenues for research. These range from complex physiological networks to the inclusion of mental health and environmental factors.

As of 2010 KORA has provided the basis for more than 130 publications in international genome research. KORA data are also the basis for the development of new approaches for the prevention of chronic diseases and for analyzing health costs and outcomes from the perspective of health economics perspective. KORA is one of the bases for the Center's participation in the German Centres for Health Research, especially in the fields of diabetes, lung disease and cardiovascular disease.

Cohort studies are observational studies. Participants are followed over a longer period and investigated as to their health status and influence of certain factors. Cohort studies are well suited for determining the onset of disease in previously healthy people, depending on genetic factors, environmental or lifestyle.

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"In our aging population chronic diseases are clearly on the rise. Population-based studies using the KORA cohort allow researchers to estimate the resulting costs and the quality of life of the patients and to determine differences between population groups – including for example differences in education. In addition, the effects of new forms of care can be determined, so that prevention programs and treatment approaches can be further improved."

Prof. Dr. Reiner Leidl —

is director of the Institute of Health Economics and Health Care Management, which together with the Institute of Epidemiology is responsible for the KORA platform.

"In Germany a large national cohort is currently being prepared. This new research platform is being established by the Helmholtz Association together with university partners. With more than 200 000 participants, it will be the largest German population-based study to date. It will give us important insights into the early stages of development of common chronic diseases such as diabetes, cancer, cardiovascular, pulmonary and infectious diseases as well as neurological disorders. KORA is an important model for the concept of the national cohort."

Prof. Dr. Dr. H.-Erich Wichmann —

is director of the Institute of Epidemiology I and spokesperson of the KORA research platform (Cooperative Health Research in the Augsburg Region).

1934
The British physician W. Burton Wood describes asbestos lung cancer for the first time in the journal The Lancet.

1948
Cold temperatures and dense fog in Pennsylvania cause 4000 additional deaths in a five-day period. Similar cases occur in London in 1952 und in New York in 1960.

1970
The U.S. Environmental Protection Agency (EPA) adopts standards on air pollution.

1997 —
Research on the uptake and effect of ultra-fine particles in the organism forms the basis for legislation in the U.S. and in the European Union.

— Future Vision

Due to increased knowledge about diseases caused by airborne pollutants, their incidence is reduced by means of preventive measures.

From Population-Based Studies to Thresholds for Ultrafine Particles

A key area of research at Helmholtz Zentrum München is the investigation of the physical and chemical characteristics of ambient particles and their biological effects. Since the early 1970s scientists at the Center have been elucidating the basic biology and later also the epidemiology of the effects of fine and ultrafine particles. With their research, they have contributed to a better understanding of the effects of fine and ultrafine particulate on health. In collaboration with the U.S. Environmental Protection Agency (EPA) they have determined the scientific basis for particulate thresholds and have laid down regulatory measures for exposure to ultrafine particles. Regulatory legislation in the U.S. and in the European Union is based on these research insights.

At the latest since the 1930s when asbestos lung cancer was first described, it has been known that particulate matter can be harmful. However, detailed knowledge was lacking on how these different kinds of particles affect health. Beginning in 1968, as a first step in making a health assessment with respect to inhaled particles, scientists of the Institute of Biophysical Radiation Research under the direction of Prof. Dr. Wolfgang Pohlit studied the uptake and dispersion of particles in the respiratory tract. They developed methods suitable for elucidating the primary mechanisms of particle deposition in different regions of the respiratory tract and their cleaning mechanisms. Using the new methods, this particle deposition could be measured and described analytically as function of the size and density of the particles and as function of breath flow and duration. The mathematical description of regional deposition developed by the Institute served as basis for the deposition model published in 1995 by the International Commission on Radiological Protection (ICRP). Today it is used independently of the analysis of the radiation risk throughout the world to estimate particle count and mass deposited in the respiratory tract.

Center scientists developed methods to elucidate particle deposition in the respiratory tract.

Coincidentally with this research, scientists at the Institute of Radiation Protection headed by Prof. Dr. Wolfgang Jacobi researchers investigated the behavior of radioactive particles in the respiratory tract of mammals and also the elimination mech-

The health effects of particulate matter depend on various physical and chemical parameters of the particles. Relevant factors include size, mass, count, surface and structure. In view of what is respirable in the lungs, the particle size of 2.5 microns and below is considered to be relevant. Ultrafine particles are smaller than 0.1 microns and can penetrate deep both into the airways and to a lesser extent into the blood.

anisms of the deposited particles from the respiratory tract – a process called clearance. The goal was to estimate the radiation burden caused by the radioactive particles in the respiratory tract. These studies on lung clearance led to the development of a model for particle dosimetry in the lung, which is recommended by the International Commission on Radiological Protection (ICRP) as standard.

In the research project Inhalation that was launched in 1986 and headed by Prof. Dr. Joachim Heyder, scientists explored the biological effect of inhaled particles. One important finding was that the long-term exposure to inhaled reactive sulfur groups is not increased if acidic aerosols are inhaled at the same time. Rather, the effect is compensated and the inhalation of acidic aerosols has no long-term consequences. The studies at the Institute of Inhalation Biology confirmed a hypothesis on the parameters relevant to the particle effect: The smaller the inhaled particles and the larger their surface, the more dangerous they can be. The oxidative stress caused by these particles plays a crucial role in a variety of biological reactions.

The expansion of many international guidelines – e.g. by the Environmental Protection Agency (EPA) in 1997 – to include separate limits for ultrafine particles with sizes below 2.5 microns takes these research results into account.

Shortly after German reunification, scientists of the Institute of Epidemiology under the direction of Prof. Dr. H. Erich Wichmann carried out extensive studies in the new states in eastern Germany on the short-term and long-term effects of pollution in children and adults. They found that respiratory symptoms in children increase with the level of exposure to airborne particles and that these symptoms decrease significantly within a few years after the ambient air quality has improved.

Further studies provided insights into the role of fine and ultrafine particles in the occurrence of asthma and of cardiovascular diseases. Ultrafine particles play an important role in the onset of the symptoms in asthma sufferers as well as in the reduction in lung function and in the amount of medication required. The effects on the cardiovascular system and on the mortality rate are influenced by both larger particles and ultrafine particles.

In the late 1990s the KORA study center in Augsburg was expanded to also be a site for environmental epidemiological research on particles. The around 20 000 participants of the KORA study and the heart attack registry containing data from 1984 to 1995 provided the basis for studying the impact of particulate on the cardiovascular system. One of the most cited epidemiological studies of 2004 was the finding that being around road traffic a few hours prior to a heart attack appeared to be a triggering factor. The study of 691 heart attack survivors from the KORA region around Augsburg showed that there was a 2.9-fold increased risk of suffering a heart attack an hour after being in traffic.

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"With our research we want to reveal correlations between particles in the ambient air and their significance for health, in order to be able to recommend effective preventive measures. As a meteorologist I am also very interested in the meteorological changes caused by climate change and how they impact health, especially how they interact with air pollutants and how the population could specifically adapt to this change."

Dr. Alexandra Schneider —

heads the working group Environmental Risks at the Institute of Epidemiology II. The focus of her research is on investigating the health effects of ambient air pollution as well as weather and climate.

1537
The doctor, alchemist and philosopher Paracelsus describes an elevated incidence of lung diseases in miners in the mining district of Joachimsthal-Schneeberg in the Ore Mountains in Saxony.

1898
The French physicists Marie and Pierre Curie discover the element radium and the radium emanation emitted by it, a radioactive gas later identified as radon 222.

1912
In Bad Kreuznach the first "radium tunnel" is opened for therapeutic inhalation of natural emissions of radon.

2005 ——

Precautionary limits and threshold recommendations for radon exposure in buildings are largely based on research conducted at the Center.

—— Future Vision

Newly developed dosimeters enable individual protection against radon.

Lung Cancer Prevention through Radon Limits

Researchers at the Center have been significantly involved in the assessment of lung cancer risk from radon and its decay products. In 1964 they succeeded in elucidating dose distribution in the lung and in making first dose estimates. The concentration of the naturally occurring radioactive noble gas radon is present in buildings in very different concentrations and causes most of the natural radiation exposure. The investigations and risk assessments of the Center have been incorporated into national and international radiation protection recommendations and have led to the preparation of improved construction guidelines, in order to reduce the number of possible deaths due to radon.

Radon is a naturally occurring radioactive noble gas which seeps from soil or building materials into the indoor air of homes and is inhaled by the residents. Its short-lived decay products attach themselves to fine dust particles. These are inhaled deep into the lungs where they are deposited on the surface of the bronchial tubes. There they emit biologically highly potent alpha radiation during their decay. The increased number of cases of lung diseases and lung cancer in miners could be partly attributed to the very high radiation doses from radon and its decay products. Early studies on lung cancer risk from radon were based on examinations of miners.

Early studies on lung cancer risk from radon were based on examinations of miners.

In 1964 researchers of the Center succeeded in elucidating dose distribution in the lung and the biophysical mechanisms underlying the damage due to radon. From this data, the Institute of Radiation Protection developed dosimetric models, which enabled precise estimates of the inhaled activity and the resulting organ dose.

Houses can also contain radon depending on the geological composition of the ground they are built on. In Germany the radiation exposure from radon in houses is about half of the average natural radiation dose of the population. Providing ventilation or implementing structural measures can reduce the radon content of the indoor air. The concentration of radon in the individual case can only be determined by actual measurements in the apartment or common areas.

Since the formation of the Earth, soils have contained naturally occurring radioactive substances. The radioactive noble gas radon is formed, for example, in the radioactive decay chains originating from uranium 238, thorium 232 and uranium 235. As gas, radon can escape through cracks and capillaries and enter into the atmosphere. Inside buildings the radon content is often many times higher than in outside air, because the noble gas accumulates there. Radon produces a series of short-lived radioactive decay products, which attach themselves to aerosol particles in the air causing high radiation exposure of the lungs when inhaled.

Between 1980 and 1984 in the Federal Republic of Germany the indoor air of 6 000 houses was measured for radon activity. On this basis, the Institute of Radiation Protection under the direction of Prof. Dr. Wolfgang Jacobi made first estimates of the radon-related lung cancer risk of the population due to living in houses. This first assessment was an extrapolation of risk values, based on epidemiological studies of highly exposed uranium miners. Two decades later it was confirmed by epidemiological studies in the general population.

For the first time in Germany, in two epidemiological studies between 1990 and 1997, the Institute of Epidemiology under the direction of Prof. Dr. H. Erich Wichmann together with Ludwig-Maximilians-Universität Munich studied the association between radon in homes and lung cancer. The studies were summarized as the German Lung Cancer Study and showed an increase in lung cancer risk correlated to the level of radon concentration in homes. An even more accurate lung cancer risk assessment was based on a combined analysis of the German study and eleven other epidemiological case control studies in Europe. Based on the cases of more than 7 000 lung cancer patients and 14 000 control persons, the increase in relative risk per 100 Bq/m³ radon concentration is estimated at 16 percent. About two percent of all cancer deaths in Europe, according to the summary, could be due to elevated concentrations of radon in homes.

In 2005 the study results were the basis for the re-evaluation of radon-related health risks by the Federal Office of Radiation Protection and the German Commission on Radiological Protection (SSK). The recommendation was to improve the guidelines pertaining to the structural requirements of houses in order to reduce the number of deaths caused by radon.

In September 2009 the World Health Organization (WHO) published a handbook on lung cancer risk caused by radon in indoor air. According to this handbook, radon is – after smoking – one of the most common causes of lung cancer. The WHO advocated action to reduce the individual risk of the affected persons. Over the longer term, the population should be protected by precautionary construction measures and through the renovation of older buildings. According to WHO recommendations, the maximum concentration of radon in old and new buildings should not exceed 100 Bq/m³.

In contrast to determining the radon concentration in the indoor ambient air, the precise determination of the radon exposure of an individual is time consuming and expensive. Hitherto, it only provides meaningful results if the measurements are taken over a period of weeks and months. As a contribution to personalized health protection, the Institute of Radiation Protection is developing a portable radon exposure meter which provides rapid determination on the individual exposure level.

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"Radon in buildings is a major environmental lung cancer risk when its concentration exceeds certain levels. Our goal is to develop measurement methods that allow faster and easier determination of the actual individual radon exposure. We thus contribute to improved personalized health protection of the population."

Prof. Dr. Werner Rühm —

heads the working group Individual Dosimetry in the Institute of Radiation Protection. Besides research on determining the individual personal radiation dose, his group develops innovative dosimeter systems for neutrons, photons and radon.

1912
The Austrian physicist and later Nobel laureate Victor F. Hess discovers cosmic radiation, explaining the conductivity of the atmosphere and the increase of gamma radiation.

1919
The airline Deutsche Luft-Reederei (DLR), a precursor to Lufthansa, begins regularly scheduled air service for passengers in Germany.

2010
According to EUROCONTROL, alone in the European airspace there are 26 000 flights per day.

2003 ——

To accurately determine the cosmic radiation exposure of their flight crews, many European airlines use EPCARD, the software program developed at the Center.

—— Future Vision

Software programs improve occupational health and safety in various fields of work.

Health Protection, Flying High

The software program EPCARD – European Program Package for the Calculation of Aviation Route Doses was developed by the Institute of Radiation Protection. With the software program, the radiation dose due to natural cosmic radiation can be determined for any flight route and flight profile. In 2003 the Federal Aviation Office and the Physikalisch-Technische Bundesanstalt (PTB), the national metrology institute, officially approved EPCARD. The program has since been used by numerous German and European airlines to determine the dose of their aircrews and helps to protect the health of pilots and flight attendants.

In conjunction with the development of civil aviation and its increasing use as a means of transport after World War II, passengers and in particular flight crews were regularly exposed to cosmic radiation in undefined amounts. Cosmic radiation from outer space penetrates the solar system, where it is at first somewhat shielded by the solar magnetic field. When approaching Earth, the cosmic rays must also overcome the Earth's magnetic field, which is especially difficult at the equator and much easier at the magnetic poles. When cosmic radiation – also known as cosmic rays – reaches the edge of the Earth's atmosphere, it interacts with air molecules and produces cascades of secondary ionizing particles. In contrast, the solar wind emanating from the sun can only overcome the Earth's magnetic field in the case of sudden solar eruptions.

Radiation exposure in aircraft is due to naturally occurring cosmic radiation.

Already in the 1970s the Institute of Radiation Protection under the direction of Prof. Dr. Wolfgang Jacobi began research on the theoretical and experimental determination of natural radiation exposure in aircraft. This exposure depends on the duration of the flight and in particular on the flight altitude, the geographical latitude of the flight route and on solar activity.

In 1990, the International Commission on Radiological Protection (ICRP) published its assessment on radiation exposure during flights. According to the report, professional pilots and aircrew are exposed to cosmic radiation doses that on average are

comparable or even higher than those of people who work with ionizing radiation in medicine and technology.

With the support of Lufthansa, the Institute of Radiation Protection with Herwig G. Paretzke as director carried out experiments to determine the radiation dose in a number of test flights. In 1994 the Neuherberg researchers for the first time presented homogenous data records on cosmic radiation exposure in civilian aviation. This served as an important basis for the discussion concerning the exposure risk of flight crews.

In 1996 the dose limits recommended by the ICRP were incorporated into European law and subsequently into national law. Since 2003, according to the German Radiation Protection Ordinance the radiation dose of aircrews must be assessed if the annual dose can amount to more than one millisievert. Since the regulations prescribe assessment of the effective dose, which includes numerous biological and physical factors, the dose values of the crews are usually not measured, but rather calculated for each flight route using software programs.

In December 2003 the program package EPCARD, developed by the Institute of Radiation Protection together with scientists of the University of Siegen to determine the radiation dose of flight personnel, was tested and subsequently approved for use by Germany's national metrology institute, the Physikalisch-Technische Bundesanstalt (PTB), and the Federal Aviation Office. The new version EPCARD.Net Professional was officially approved in April 2010.

To explore the influence of solar flares on the radiation dose more precisely, in 2007 the Center installed a measuring unit at the Koldewey Station of the Alfred Wegener Institute for Polar and Marine Research in Spitzbergen, Norway. The aim of the project is to more exactly measure cosmic radiation on aircraft and crews during flight and thus to increase health protection for flight crews with respect to cosmic radiation.

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A simplified version of EPCARD is available at www.helmholtz-muenchen.de/epcard-portal/

The effective dose is a dose quantity used to assess the radiation exposure of individuals. It is calculated as a weighted sum of equivalent doses to all relevant tissues and organs, taking into account their different sensitivity to ionizing radiation. Equivalent dose in an organ or tissue is sum performed over absorbed doses of all types of radiation involved, taking into account their different biological effectiveness. Its unit is joule per kilogram, J / kg, with special name sievert (Sv).

"EPCARD, the software package we developed, can determine the exposure of aircrews to cosmic radiation – as a rule very precisely. Our measurements of the frequency and impact of solar flares on the radiation dose serve to constantly improve the calculation model and also take exceptionally rare events into account."

Vladimir Mares —

is a physicist in the research group Individual Dosimetry at the Institute of Radiation Protection. The group studies the dosimetric significance of cosmic radiation, and the group's research results are incorporated into the EPCARD software.

1912
The German chemist Fritz Klatte obtains a patent for the production of polyvinyl chloride (PVC).

1939
Paul Hermann Müller discovers the insecticidal properties of DDT. Nine years later he receives the Nobel Prize in Medicine for this discovery.

2004
The Stockholm Convention restricts the production and use of polychlorinated biphenyls, dibenzo-p-dioxins and dibenzofurans as well as nine pesticides, among them DDT.

1971 —

Neuherberg scientists help shape the new field of environmental chemistry and establish methods for predicting and assessing the environmental behavior of chemical substances.

— Future Vision

Innovative methods and technologies enable insights into metabolic processes and element cycling in ecosystems.

The Invention of Environmental Awareness

Scientists at what is today Helmholtz Zentrum München have given important impulses for protecting the biosphere from industrial chemicals. Since 1969, the world's first institute of ecological chemistry has been formulating criteria for assessing the effects of chemicals in natural cycles and for predicting their behavior. The pioneering methods have enabled fast and reliable testing of chemical substances as to their environmental compatibility and the determination of threshold values for the respective environmental burden. The research results have provided important contributions to environmental legislation in Germany and have contributed to the harmonization of regulations on environmental chemicals in OECD countries. Today changes are investigated at the molecular level, with metabolomic biomarkers enabling the early detection of impaired functions.

Advances in synthetic chemistry led to the widespread use of chemicals such as DDT as an insecticide. Biological effects could not be estimated beforehand. However from 1969 on, the Center forged ahead into new territory by applying ecological approaches to the presence of chemicals in the environment: In this year, the world's first Institute of Ecological Chemistry was incorporated into the Center. Beginning in the 1960s, the Institute's founder, Prof. Dr. Friedhelm Korte, developed innovative strategies for the study of the behavior and fate of chemicals in the environment. In the early stages of the emerging environmental discourse scientists at the Center increasingly focused on the environmental aspects of chemistry and were among the first to use the term "environmental chemicals".

The Center was substantially involved in the first major survey on the environment, which formed the basis of the environmental program of the Federal Government.

In the early 1970s the Center was substantially involved in the first major survey on the environment, which formed the basis of the environmental program of the Federal Government which was adopted in 1971. The main topics conceived for this survey on the occurrence, transformation and fate of chemicals in the environment were definitive for the research activities undertaken worldwide in this field during the following two decades.

According to the Environmental Action Program of the Federal Government of 1971, environmental chemicals are substances that are placed by human intervention into the environment and can occur in concentrations that can pose a risk to living organisms, especially humans. They are defined in the German Chemicals Act as environmentally hazardous substances: substances or preparations, which by themselves or via their conversion products can change the characteristics of the ecosystem, i.e. of water, soil or air, climate, animals, plants or microorganisms, in such a way that the environment can be endangered.

From 1976 on the concept of eco-toxicological profile analysis developed at the Center was confirmed in experiments. Simple experimental methods enabled researchers to establish a priority list for the screening of environmental chemicals and thus to identify potentially environmentally hazardous substances.

The Chemicals Act, which entered into force in Germany in 1980, for the first time mandated studies to assess health risks and eco-toxicological impact prior to the introduction of new substances on the market. The strategies and criteria catalogues developed at the Center to assess chemicals were incorporated into the regulations. The definition of the term environmental chemicals was adopted by the environmental protection programs of the Federal and State Governments.

The studies showed an immediate impact of the uptake and accumulation of pentachlorophenol (PCP), a chemical mainly used in wood preservatives against fungal infestation, in part also in closed rooms. Case studies and tests carried out in model rooms showed the various ways the substance can enter into the human body. The first findings on indoor pollution with PCP were published in 1975 and led to a restriction of its use in 1977. This was followed by a prohibition of indoor use in 1985 in the U.S. and subsequently in Germany in 1989.

In order to identify long-term changes in environmental quality at an early stage and to assess trends proactively, the Center proposed the establishment of a tissue bank. This environmental specimen bank initiated by the Center in the 1980s has since become a standard instrument of environmental monitoring and has existed since 1980 as environmental specimen bank under the auspices of the Federal Government.

In the 1990s the Institute of Ecological Chemistry headed by Prof. Dr. Antonius Kettrup intensified its research activities concerning the release of undesirable substances during technical processes. Under the heading "Process-integrated environmental protection", the Institute developed analyses of complex life cycles of new products. Using the example of recycling methods or the production of printed circuit boards, it developed new approaches to reducing harmful emissions and showed that sustainable use of resources and "green chemistry" are not only environmentally friendly but also provide economic benefits.

Industrial processes release many substances which are converted into biologically active substances in the environment. To carry out their eco-toxicological studies, the researchers use model ecosystems that are as realistic as possible. Special emphasis is placed on the investigation of halogenated persistent organic compounds and hormonally active substances and organometallic species.

For effective protection of human health from chemicals in the environment, researchers are increasingly focusing on the underlying mechanisms of how the chemicals act and react. Using new high-resolution methods, researchers led by PD Dr. Philippe Schmitt-Kopplin are investigating this activity on the ecosystem and organism levels, but also at a molecular level. The goal is to better understand biogeosystems to enable the sustainable use of the resources of our ecosystems for the benefit of mankind.

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"We want to elucidate molecular interactions of substances in biogeosystems and from these derive metabolomic biomarkers for the early detection of changes. Sensitive biomarkers are a key to developing preventive strategies against current and future harms to environment and human health."

PD Dr. Philippe Schmitt-Kopplin —

heads the Research Unit Biogeochemistry and Analytics at the Institute of Ecological Chemistry. One focus of his work is the study of complex processes and biogeochemical cycles in ecosystems.

1845
A blight caused by the fungus Phytophthora infestans results in successive failures of the potato crop in Ireland. One million people die in the Great Famine, and another two million emigrate to the United States.

1858
Julius Kühn writes the first textbook on plant pathology – "The Diseases of Cultivated Plants, Their Causes and Prevention" (in German).

1980
Robert Furchgott discovers a signaling molecule responsible for blood vessel dilation. Working independently, Louis Ignarro and Ferid Murad identify it as nitric oxide in 1986. The three U.S. pharmacologists share the Nobel Prize in Medicine.

2007 ——

Researchers of the Center develop sustainable pesticides on the basis of innate plant immunity.

—— Future Vision

The endogenous defense mechanisms of plants form the basis for innovative and sustainable concepts of plant protection.

Sustainable Plant Protection through Improved Self-Defense

Research activities at the Institute of Biochemical Plant Pathology focus on deciphering the mechanisms of plant defense against pathogens. From 1996 on, the scientists have been significantly involved in clarifying the role of the signaling molecule nitric oxide in wound-healing and in defense and regulatory processes in plants. In 2007 synthetic antimicrobial peptides for the defense against pathogens were registered for a patent. The scientists are also studying the use of plant activators – so-called biocontrol agents, which are often of bacterial or fungal origin – for inducing plant resistance. The goal is to develop new ways to utilize natural plant immunity for plant protection.

Industrialization led to new types of air pollution, causing extensive damage to forests in the 1970s and a decade later resulting in "Waldsterben", a German loanword meaning forest dieback. Early in the 1980s, scientists at the Center began to study the mechanisms underlying the effects of air pollutants on plants. Supporting this research were observations linking damage to forest ecosystems to a variety of environmental factors. Waldsterben became a headline issue that was much debated throughout Europe. In 1985 walk-in exposure chambers were constructed in Neuherberg, allowing the first reproducible long-term experiments on plants under controlled environmental and climatic conditions. In the years that followed, the chambers were supplemented by solar simulators to study UV damage, a clean-air greenhouse for long-term observations as well as open field research and lysimeter facilities. The Neuherberg environmental simulation facilities, in conjunction with working groups of regional and national research institutions, provide important impulses for environmental research on plants.

In 1994 the molecular mechanisms of ozone defense were elucidated in studies of tobacco plants.

Research activities at the Institute of Biochemical Plant Pathology under the direction of Prof. Dr. Heinrich Sandermann focused on molecular changes caused by environmental stress such as increased ozone or UV levels. In 1994 the molecular mechanisms of ozone defense responses in tobacco plants were described. Likewise in 1994, based on the analysis of stress molecules, ozone-related tree damage was

Nitric oxide is a colorless and poisonous gas with the formula NO. Its importance for physiological processes was discovered in the 1980s. NO is involved as a messenger molecule in the regulation of dilating blood vessels, the immune activation of macrophages, modulation of the central nervous system and the regulation of programmed cell death. In recent years, the role of NO in the induction of plant defense against microbial pathogens has been partially elucidated.

identified as a delayed response to previous harmful influences: the so-called "memory effect".

How plants deal with harmful environmental influences continued to be one of the key issues of plant ecosystem research at the Center. Researchers at the Center contributed substantially in the late 1990s to the discovery of the role of nitric oxide (NO) in plant defense and its role as signaling molecule in the activation of the plant immune system.

In the following years, the Institute of Biochemical Plant Pathology, headed by Prof. Dr. Jörg Durner, continued to study the different steps of plant defense. Using Arabidopsis and barley as model plants, the researchers focused on elucidating the role of NO in plant defense in order to analyze and understand the mechanisms of plant immune defense down to the molecular level. In principle, plant immune response has many similarities to the immune response in humans and animals. The presence of a pathogen is detected by the plant, and the information is passed into the cells, where antibodies against the pathogen are produced.

Plant pests and plant protection have been known since antiquity, but it was first the large monocultures that brought about the widespread pest infestations that resulted in major famines. Recent scientific evidence has suggested that plants are able to defend themselves against pests. But how do plants recognize that they are challenged by the attack of a pest, and how are the plant's defense mechanisms triggered? In 2004 a research group at the Institute of Biochemical Plant Pathology demonstrated that the model plant Arabidopsis thaliana – by a mechanism similar to that of mammals – reacts to contact with bacteria by activating its innate immune response: Lipopolysaccharides (LPS) on the surface of bacteria serve the plant as a recognition principle and activate a cascade of defense mechanisms.

The role of the signaling molecule nitric oxide in this mechanism was finally clarified by the scientists in 2010. Once again using Arabidopsis, they showed in detail how NO triggers the plant defense cascade. Here the molecular switch is the protein NPR1, which in the presence of a pathogen decays into a form capable of responding and migrates into the cell nucleus, where it activates the defense genes. NO serves as a signal for the translocation of NPR1 into the cell nucleus and as a trigger for the defense mechanisms.

From the basic knowledge gained on plant immune defense, the researchers seek to develop new approaches for plant protection. The particular strength of molecular plant research at Helmholtz Zentrum München lies in the close collaboration of researchers engaged in the fields of plant biochemistry and microbial ecology in soil and water. Their aim is to develop sustainable production systems and to contribute to securing important ecological resources.

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"In the future, plants will become increasingly important – not only as a source of food and fodder – but also as a source of valuable chemical compounds and renewable raw materials for bioenergy. At the same time, the increasing demand will be restricted by the limited availability of good soil and water and the lack of plant varieties with high resource use efficiency. Based on the traditional strengths of the Center such as molecular phenotyping or plant-microbe-environment interactions, we are developing systems biological approaches for sustainable crop production."

Prof. Dr. Jörg Durner ——

is director of the Institute of Biochemical Plant Pathology, which is developing new approaches for sustainable crop protection and production.

1938
The German chemists Otto Hahn and Fritz Strassmann first demonstrate the fission of uranium atoms by bombardment with neutrons.

1942
The Italian nuclear physicist Enrico Fermi accomplishes the first artificial, self-sustaining nuclear chain reaction for the production of plutonium.

1960
In Kahl the first German nuclear power plant is connected to the grid.

1966 ——

On behalf of the Federal Government, the Center begins research on the safe permanent disposal of nuclear waste in the Asse Mine.

—— 2009

The responsibility for the Asse Mine is transferred to the Federal Office of Radiation Protection.

The Asse Mine – Lessons for a Permanent Nuclear Waste Repository?

Helmholtz Zentrum München operated the Asse facility as a research mine from 1966 to 2008. On behalf of the Federal Republic of Germany the Institute of Underground Disposal developed and studied methods for the permanent disposal of nuclear waste in the salt dome located in Lower Saxony. The results of this research have proven significant – also from an international perspective – for finding a concept for permanent nuclear waste disposal in deep geological formations. Research activities in the Asse Mine ended in 1995. Since the beginning of 2009 the Asse Mine has been operated by the Federal Office for Radiation Protection (BfS) in accordance with the provisions of nuclear law.

In the 1960s, in connection with the peaceful use of nuclear energy, a broad public discourse took place on the issue of how to deal with nuclear waste. No permanent waste disposal sites existed at this time. Deep underground disposal in salt domes was considered a promising option, and the goal of applied research was to make progress in finding a solution to this waste disposal problem. By agreement between the Federal Ministry for Scientific Research (BMwF; now the Federal Ministry for Education and Research, BMBF), the German Atomic Energy Commission and the Federal Institute for Soil Research, the former salt mine Asse II was selected as a research site. On behalf of the CDU-led Federal Government, the new-founded Gesellschaft für Strahlenforschung (the former name of Helmholtz Zentrum München) acquired the Asse salt mine in 1965.

The results of research activities in the Asse Mine have been published in numerous publications and have received international recognition.

Research activities began in 1966 to find a solution for the safe permanent disposal of radioactive waste. The geodetic survey and rock monitoring program was started within the mine complex, and in August 1966 the first heater experiment 1a at a depth of 490 meters was started to simulate the effects of heat generated by the radioactive waste on the salt rock.

To carry out the scientific studies, the Gesellschaft für Strahlenforschung founded the Institute of Underground Disposal, based in Clausthal-Zellerfeld. The Operational

The research activities in the Asse Mine have received general recognition. The results have influenced national and international concept planning for the permanent disposal of radioactive waste in deep geological formations and have made major contributions to scientific and technological knowledge.

After a change of responsibility at the federal ministerial level, the operatorship of the Asse Mine was transferred to the authority responsible according to nuclear law, the Federal Office for Radiation Protection (BfS), at the beginning of 2009. The BfS is considering various options for decommissioning the mine.

Department of Underground Disposal, based in Wolfenbüttel, had the task of operating the mine and developing and assessing emplacement techniques for radioactive waste.

In April 1967 the emplacement of low-level radioactive waste in various former mining chambers was begun. From August 1972 to January 1977 intermediate-level radioactive waste was stored in a specially prepared chamber. All emplacements were based on permits issued by the competent national authorities in Lower Saxony in compliance with the then applicable laws. A total of 125 787 waste canisters were emplaced in Asse II, of which 124 494 contained low-level radioactive waste. In addition, from 1972 to 1977, 1293 canisters containing intermediate-level radioactive waste were transported using a newly developed shielding and remote control system and lowered into storage chamber 8a at a depth of 511 meters.

In 1978 the existing emplacement license expired. The Federal Government and the State of Lower Saxony decided at ministerial level to continue operation of Asse Mine II exclusively for research and developmental work on the safe permanent disposal of radioactive wastes.

Research of international standing

From 1979 on, the research carried out in Asse concentrated on mining and engineering methods and specific safety-related issues. The main focus was on the analysis of geological and geochemical relationships and their petrophysical parameters and rock mechanical processes. Seminal studies were carried out on the secure sealing of permanent waste sites in geological formations, i.e. the creation of a prototypical sealing dam against the inflow of saline solutions and the filling and sealing of boreholes, chambers and shafts.

Similarly, simulation experiments were carried out to investigate the effect of heat and radiation emanating from high-level radioactive waste. Starting in early 1966, simulations were conducted using electric heaters to determine how heat affected the rock salt. In a joint German-American endeavor carried out from 1983 to 1985, the scientists of the Institute of Underground Disposal conducted an underground project for the first time in Europe to measure the combined effect of heat and radiation on the surrounding salt rock. In a two-year experiment, electric heaters and cobalt-60 sources were emplaced in two boreholes in an experimental site 800 meters deep. After the end of the experiment, the cobalt 60 sources were retrieved and transported back to the manufacturer in England.

The results of research activities in the Asse Mine have been published in numerous publications and have received international recognition. These findings have influenced planning for permanent repositories in Germany, France, Switzerland and the U.S. In 1995, due to disagreements about the funding of the large-scale experiments, the Institute of Underground Disposal was discontinued. The scientists were transferred to the new founded Department of Nuclear Repository Safety of the Gesellschaft für Anlagen- und Reaktorsicherheit (GRS).

Closure prepared

Thus, the research and development work at Asse came to an end, and activities focused on a safe closure of the mine. The technical aspects of closure present a special challenge, since the slope stability of the mine is only ensured for a limited time. The inflow of saline solution dripping from the overburden rocks, first observed in 1988, is one of the factors responsible for this. It is caused by the previous use of the facility as a salt mine. The large cavities and the long period the mine stood open have led to a loosening of the rock and as a consequence, have enabled fluids to enter the mine from the overburden rocks.

As far as mining and radiation protection techniques are concerned, the inflow of saline solution was always under control and in compliance with legal limits at all times. The State Office for Mining, Energy and Geology (LBEG) as responsible mining authority received regular reports about the development of the saline solution inflow and the presence of contaminated saline solutions in the mine. The Center always fulfilled its obligation to inform the authorities and also informed the general public at various events.

From 2002 on, the Center developed a concept to introduce a protective fluid into the remaining chambers following a backfilling with solid material. The request for final closure of the mine was submitted to the State Office for Mining, Energy and Geology in January 2007. The request contained a closure plan and a safety report verifying the long-term safety of the mine.

In 2008 the Federal Ministry of Education and Research (BMBF) and the Federal Ministry for the Environment decided on a change of operatorship from Helmholtz Zentrum München to the Federal Office for Radiation Protection (BfS). Since the transfer of the responsibility for the Asse Mine to the BfS, which became effective on January 1, 2009, the mine has been considered a final repository and has been treated procedurally according to nuclear law. This required an amendment to the Atomic Energy Act, which the German Bundestag passed on January 29, 2009 and the Bundesrat passed on February 13, 2009. Since this change in the law, the closure of Asse can be implemented according to the provisions of nuclear law and is subject to a plan-approval procedure laid down in this law.

In the course of the change of operatorship, the employees were transferred to the Federal Office for Radiation Protection by transferring their work contracts to the newly founded Asse GmbH – Company for the Operation and Decommissioning of the Asse II Mine. At the same time all operationally relevant documents were officially handed over to the Office for Radiation Protection.

Timeline of Asse

1906 Start of operations to bore the Asse II shaft

1909 Start of potash mining at Asse II

1916 Start of rock salt mining

1925 End of potash mining due to the decline of the German potash industry following World War I

1928 Liquidation of mining operations at Asse; entire property and assets sold to Burbach Kaliwerke AG

1964 End of rock salt mining at Asse for economic reasons

1965 The Gesellschaft für Strahlenforschung (GSF) acquires the Asse salt mine on behalf of the Federal Government

1966 The newly established Institute of Underground Disposal, based in Clausthal-Zellerfeld and the Operational Department of Underground Disposal, based in Wolfenbüttel, begin research in the field of underground disposal of radioactive wastes

1967 Start of disposal of low-level radioactive waste

1972 Start of disposal of intermediate-level of radioactive waste

1978 The last disposal permits expire; end of emplacement of low and intermediate-level radioactive waste in the Asse Mine

1979 The Federal Government and the State of Lower Saxony decide to use the Asse salt mine exclusively for research and development work relevant to the safe permanent disposal of radioactive waste

1992 The Federal Ministry of Research and Technology (BMFT) announces that the large-scale experiments carried out in the Asse Mine will no longer be financed through project funds

1995 The Institute of Underground Disposal is dissolved; the backfilling of the mine with residual salts is approved

1995 Start of backfilling of the old mining chambers in the south flank of the Asse mine with residual salts of the former potash mine Ronnenberg

2004 The backfilling of the chambers in the south flank is completed; the backfilling of other areas of the mining facility continues

2005 Handover of the final operating plan with security report to the mining authorities

2006 The final operating plan is conditionally approved by the State Office for Mining, Energy and Geology

2007 The request for final decommissioning of the mine is submitted to the State Office for Mining, Energy and Geology

2008 A resolution for an operatorship transfer from Helmholtz Zentrum München to the Federal Office for Radiation Protection (BfS) is adopted by the Federal Cabinet

2009 Effective January 1st, the Federal Office for Radiation Protection takes over operatorship of the Asse Mine

2009 The Bundestag and the Bundesrat adopt an amendment to the Atomic Energy Act mandating the decommissioning of the Asse Mine according to nuclear law

Infection and Immunology Research

at Helmholtz Zentrum München since 1960

1964
The Institute of Hematology is founded

1966
First steps to research allogeneic bone marrow transplants for the treatment of leukemia patients

1970
Foundation of the Department of Immunohematology, later Institute of Immunology

1973
The Institute of Pathology discovers virus-like particles in radiation-induced osteosarcomas

1975
First successful bone marrow transplant in Germany

1977
Worldwide first clinical application of T-cell depletion for weakening the immune reaction

1979
Procedures for the removal of leukemia cells from bone marrow allow for autologous bone marrow transplants

1981
Establishment of the Service Unit Monoclonal Antibodies at the Institute of Immunology

1984
First molecular-biological study of the role of endogenous proviruses in the development of tumors

1986
The newly established Research Unit Molecular Cellular Pathology launches research into the pathogenesis and treatment of HIV diseases

1988
The Institute of Immunology starts working with recombinant antibody technology and the production and preclinical trial of bispecific antibodies

1988
First successful use of adoptive immunotherapy against leukemia relapse

1989
Foundation of the Institute of Clinical Molecular Biology and Tumor Genetics

1989
Leibniz Research Award for Georg Bornkamm

1990
The Institute of Clinical Molecular Biology and Tumor Genetics develops a screening procedure for tumor promoters, based on the Epstein Barr Virus

1991
Foundation of the Institute of Molecular Virology

The Future

Immunological approaches lead to gentler and more effective therapies against tumors and viral diseases

2010

Helmholtz Zentrum München becomes a partner of the German Centre for Infection Research (DZIF)

2009

An antibody effective against cancer cells, based on immunological research at the Center, receives approval by the European Medicines Agency EMEA

2008

The Institute of Virology shows that HI viruses multiply not just in the brain's astrocytes but also in the neural precursor cells

2008

The Service Platform Monoclonal Antibodies is involved in the identification of all proteins of the human herpes virus

2007

The world's first phase III trial proves efficiency of hyperthermia and chemotherapy for the treatment of connective tissue sarcoma

2005

Evaluation of MVA as an alternative vaccine against smallpox (variola)

2004

Vaccine against HIV on the basis of a genetically modified Vaccinia virus is tested in a clinical phase I trial

2004

Foundation of the joint Immune Monitoring Group by the Institutes of Molecular Immunology and Molecular Virology

2000

Erwin-Schrödinger Award for Director of the Service Platform Monoclonal Antibodies, Dr. Elisabeth Kremmer (together with Martin Lipp, Reinhold Forster, MDC, and Eckhard Wolf, LMU)

1998

The Institute of Clinical Molecular Biology and Tumor Genetics successfully produces a complete clone of a herpes virus for the first time

1998

Foundation of the Institute of Molecular Immunology

1998

Spin-off of Trion Pharma GmbH with the aim of further developing a family of antibodies for tumor therapy, originating at the Institute of Immunology

1997

The Institute of Molecular Virology develops a test system for analyzing mutated measles viruses

1995

The Service Unit Monoclonal Antibodies becomes the Service Platform Monoclonal Antibodies

1995

Based on the Vaccinia virus, the Institute of Molecular Virology develops a vector system for creating vaccines

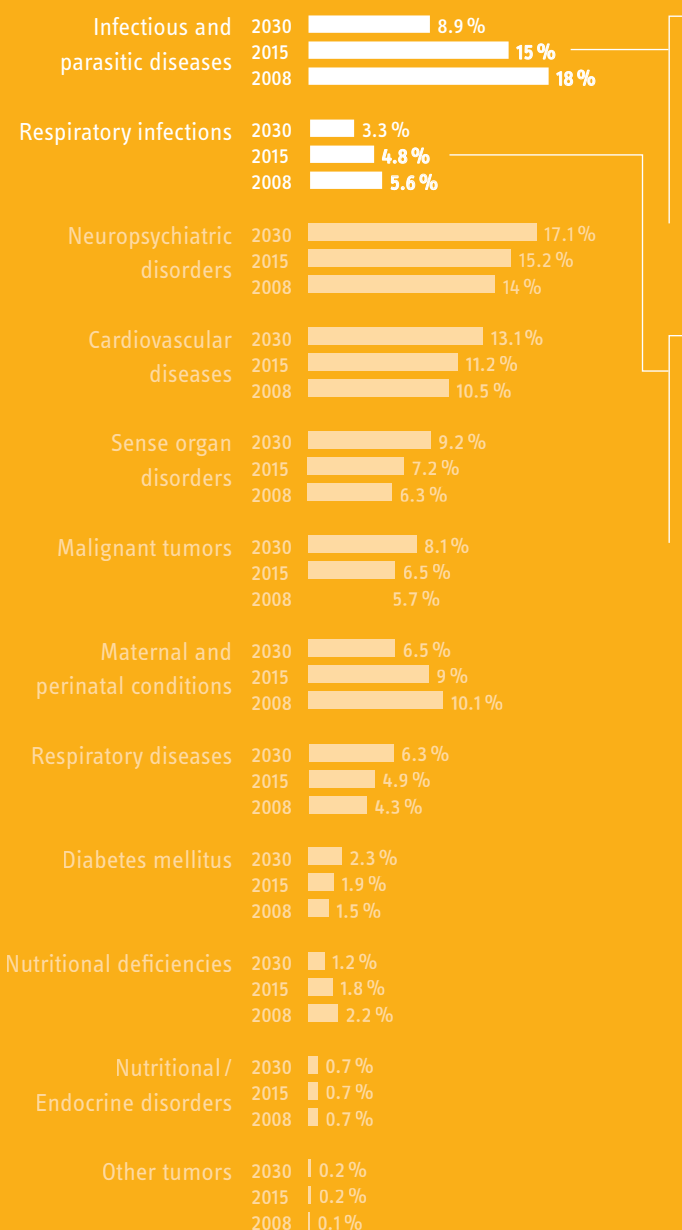
1992

The Institute of Molecular Virology begins to research the role of retroviruses in human diseases

Partner of the German Centre for Infection Research (DZIF)

Helmholtz Zentrum München

Causes of the Global Burden of Disease 2008 to 2030: A Better Grip on Infectious Diseases



	2008	2015	2030
HIV/AIDS	4.4 %	4.4 %	2.5 %
Hepatitis B (d)	1.1 %	1.1 %	0.1 %
Hepatitis C (d)	0.1 %	0.0 %	0.0 %
Lower respiratory infections	5.4 %	4.6 %	3.2 %
Upper respiratory infections	0.1 %	0.1 %	0.1 %
Otitis media	0.1 %	0.1 %	0.0 %

These projections show the share of the overall burden of disease in percent, stated in DALYs.

One DALY (Disability Adjusted Life Year) is a year of healthy life lost to disability. The "DALY" figure aims to not just summarize the mortality, but also the impairment of the normal life, free of complaints, through an illness, by providing a comparable measure.

Source: Projections of mortality and burden of disease, world health organisation, baseline scenarios 2008, 2015, 2030
www.who.int/healthinfo/global_burden_disease/projections/en/index.html

The **German Centre for Infection Research (DZIF)** was initiated by the Federal Ministry of Education and Research as part of a competition for setting up German Centres for Health Research. It aims to pool the expertise of leading scientists and to jointly develop new strategies to combat pathogens. Based on the joint application of Helmholtz Zentrum München, Technische Universität München, Ludwig-Maximilians-Universität and the Institute of Microbiology of the German Bundeswehr, Munich was selected as one seven partner locations.

"As a partner of the German Centre for Infection Research, we aim to successfully combat viral diseases. Our research focuses on chronic infectious diseases such as hepatitis and secondary diseases. This includes in particular viral hepatitis and hepatocellular carcinoma, HIV and AIDS as well as human endogenous retroviruses, whose pathogenetic relevance is still unclear. Based on molecular studies, we develop innovative diagnostic and therapeutic concepts, using viruses as therapeutic instruments and establishing strategies that aim to prevent viral diseases or the development of tumors."

Prof. Dr. Ulrike Protzer is Director of the Institutes of Virology at Helmholtz Zentrum München and at Technische Universität München in the Klinikum rechts der Isar. As an internist and specialist for microbiology, virology and infection epidemiology, she coordinates the contributions of Helmholtz Zentrum München to the German Centre for Infection Research.

Molecular Mechanism Prevents Autoimmunity

"We want to understand the molecular mechanisms that help mature B cells and T cells to distinguish foreign antigens from the body's own structures in order to develop fine-tuned intervention strategies for autoimmune or immune diseases. These strategies need to selectively modulate the immune system by repressing only unwanted immune responses or inducing desirable immune responses."

Dr. Vigo Heissmeyer

since 2005 Group leader of the research group Molecular Programmes of T-cell Tolerance at the Institute of Molecular Immunology — **since 2008** Habilitation candidate in Biology, Ludwig-Maximilians-Universität Munich — **2001–2005** Postdoc, Harvard Medical School, Center for Blood Research — **2000–2001** Postdoc, Max-Delbrück-Center for Molecular Medicine, Berlin

Cooperation Partners / Authors

Helmholtz Zentrum München Elke Glasmacher, Kai P. Höfig, Katharina U. Vogel, Nicola Rath, Lirui Du, Christine Wolf, Elisabeth Kremmer, Vigo Heissmeyer — **Northwestern University Evanston, Illinois** Xiaozhong Wang

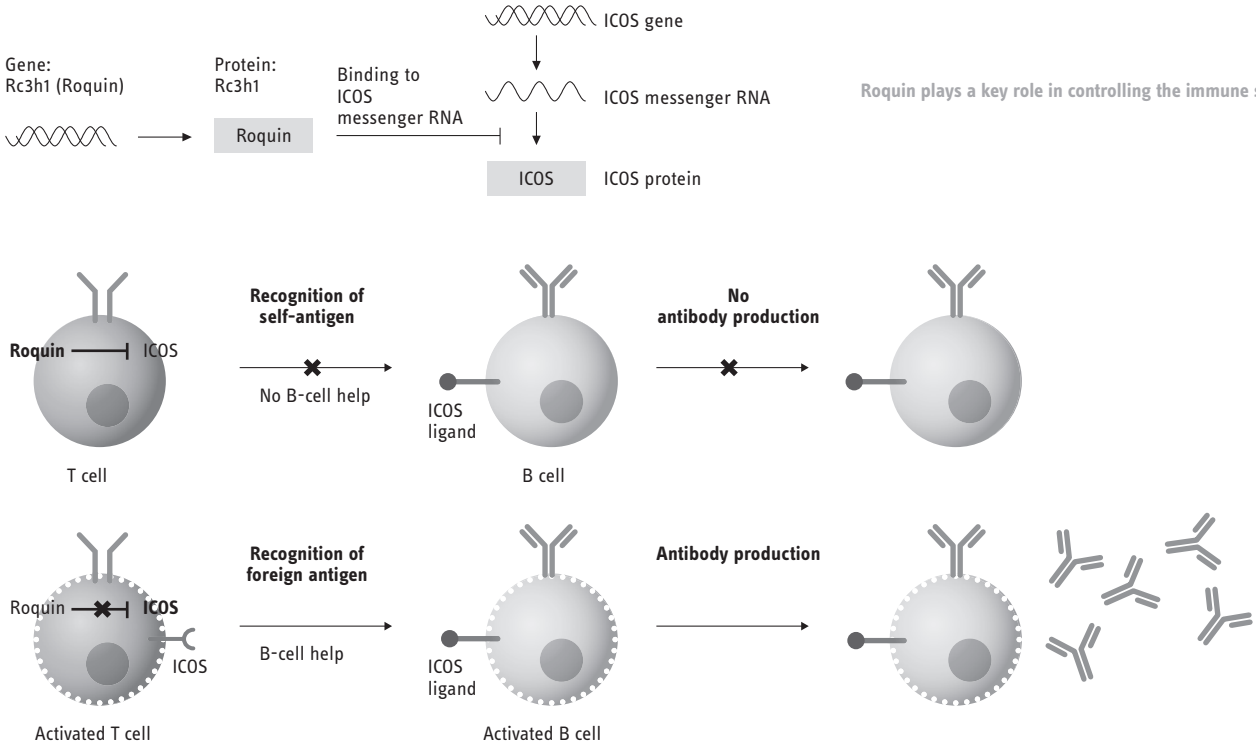
In a healthy organism, the roquin protein protects against harmful self-attacks by the body's own immune system. A research group of Helmholtz Zentrum München has succeeded in elucidating important molecular steps underlying this protective mechanism. The results contribute to the understanding of autoimmune diseases and to developing effective treatment approaches.

Autoimmune diseases can be caused by a partial loss of function of the roquin protein. In a healthy organism roquin prevents autoimmunity. The research group led by Vigo Heissmeyer of the Institute of Molecular Immunology has elucidated the mechanisms underlying the protective function of roquin.

Roquin controls the expression of the inducible costimulator gene (ICOS). Without sufficient roquin function, the T cells of the immune system go on high alert and unrestrainably produce ICOS proteins on their cell surface. This in turn stimulates other white blood cells, the B lymphocytes, in a process of so-called "B-cell help". Normally, B cells produce antibodies against pathogens and thus combat infections. However, if roquin activity is insufficient, T cells are formed with an increased amount of ICOS. These helper T cells can induce the B cells to produce antibodies against the body's own tissue. Severe autoimmune diseases are the consequence.

The scientists showed that roquin counteracts this overproduction by binding to the ICOS mRNA, thus inducing mRNA decay. Normally, the mRNA transports the blueprint for the ICOS protein from the DNA in the cell nucleus to the ribosomes in the cytoplasm, where protein synthesis takes place. However, if roquin bound to the mRNA, this was prevented. There were areas in the cytoplasm of T cells in which roquin was present in particularly high concentrations – the so-called processing (P)-bodies. These are defined structures within a cell that play an important role in mRNA decay.

How Roquin Protects against an Attack of the Immune System



Roquin plays a key role in controlling the immune system.

The research group's findings turned out to be a surprise. It was previously assumed that microRNAs play an essential role in repressing ICOS gene expression. MicroRNAs are very small RNA molecules that bind to a particular element of the target-mRNA, thereby repressing the translational process in which the mRNA is "read and translated" on the ribosomes and the proteins are synthesized according to the genetic code.

The research group expects that roquin-mediated repression of ICOS as well as of additional targets plays a still unknown role in various chronic immune diseases such as allergies and in T-cell-mediated autoimmune diseases such as type 1 diabetes.

To date, the lack of tolerance of B cells and T cells in patients with autoimmune diseases cannot be restored therapeutically. Currently used drugs usually repress the entire immune system and often have serious side effects. Inducing a therapeutically effective immune response against a tumor or reactivating immune cells to target a chronic infection is equally difficult. These responses, which are present in healthy individuals, are repressed in patients due to misguided tolerance mechanisms. Targeting roquin could provide a new approach to solving this problem in the future.

About five percent of all people are affected by autoimmune diseases. Their immune system attacks the body's own structures and destroys them. This often leads to diseases with severe symptoms. Diabetes mellitus type 1 is one of these autoimmune diseases, along with lupus erythematosus, rheumatoid arthritis and multiple sclerosis.

Original Publication

Elke Glasmacher et al.: Roquin binds inducible costimulator mRNA and effectors of mRNA decay to induce microRNA-independent post-transcriptional repression. Nature Immunology 11 (2010) 725-733 | doi:10.1038/ni.1902

Uniform Nomenclature Developed for White Blood Cells

"The newly discovered cells will become integral elements in the diagnosis of infectious and inflammatory diseases. Researchers are already focusing on them as a target for therapeutic treatments. The nomenclature, which has now been established, will help to clearly define the different cells and thus foster further development of this field."

Until recently the newly discovered subgroups of white blood cells were known under different names. A specially developed nomenclature for the diverse group of leukocytes now ends communication problems among scientists.

Prof. Dr. Loems Ziegler-Heitbrock

since 2007 Head of the EvA Study Center at Helmholtz Zentrum München, coordinator of the EU project EvA: Markers for Emphysema vs. Airway Disease in COPD — **2001–2006** Chair of Immunology, University of Leicester, UK — **1981–2000** Research associate and later professor at the Institute of Immunology of Ludwig-Maximilians-Universität Munich — **1979–1980** Postdoc, University of Minnesota, Minneapolis, USA — **1976–1977** Resident physician, Buxtehude and the Hamburg University Medical Center

Cooperation Partners / Authors

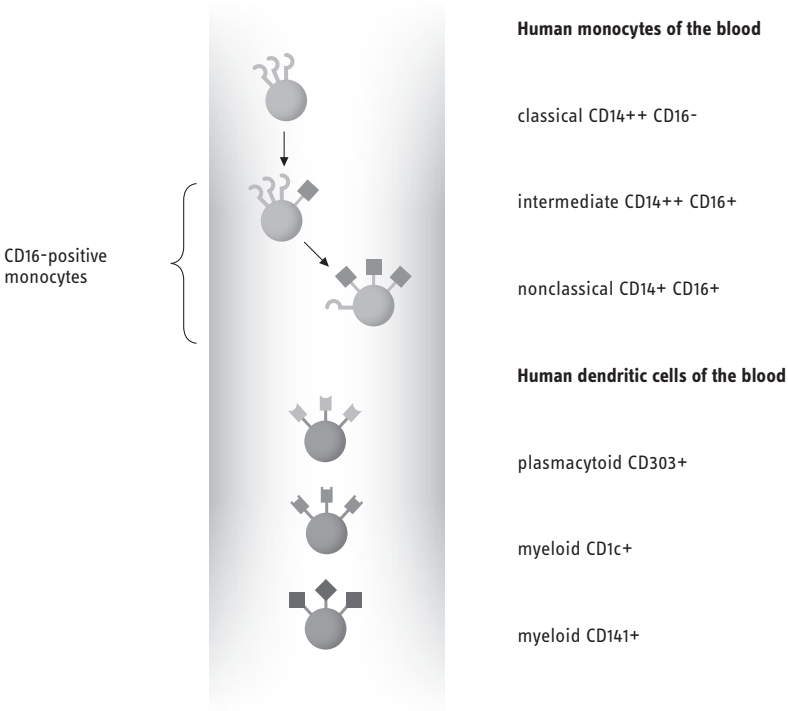
Helmholtz Zentrum München and University of Leicester Loems Ziegler-Heitbrock — **Université de Montreal** Petronela Ancuta — **Macfarlane Burnet Institute for Medical Research, Melbourne** Suzanne Crowe — **Université de la Mediterrane, Inserm und CNRS, Marseille** Marc Dalod — **Universität Gießen** Veronika Grau — **Anzac Research Institute, Sydney** Derek N. Hart — **Erasmus University Medical Center, Rotterdam** Pieter J. M. Leenen — **University of Texas** Yong-Jun Liu — **University of Oxford** Gordon MacPherson, Jonathan M. Austyn — **Mount Sinai School of Medicine, New York** Gwendalyn J. Randolph — **Ludwig-Maximilians-Universität Munich** Jürgen Scherberich — **Miltenyi Biotec, Bergisch Gladbach** Jürgen Schmitz — **The Walter and Eliza Hall Institute of Medical Research, Melbourne** Ken Shortman — **University of Brescia** Silvano Sozzani — **Medical University of Vienna** Herbert Strobl — **Jagiellonian University Medical College, Krakau** Marek Zembala — **University of Würzburg** Manfred B. Lutz

The variety of names for the different subpopulations of white blood cells had even confused scientists. That is why Loems Ziegler-Heitbrock of Helmholtz Zentrum München, together with an expert team from Europe, Australia and the USA, developed a new nomenclature. It employs the standard method of naming tissues and cell types, using only a single name and specific markers providing additional information. The International Union of Immunological Societies (IUIS) is already using these uniform names.

According to the new nomenclature, monocytes are divided into classical, intermediate and nonclassical categories. For the characterization of the types the markers CD16 and CD14 have proven useful. The classical monocytes are synonymously designated as CD14++CD16-. This means that large amounts of the marker CD14 are present on their surface, but that no CD16 is produced. This cell type has been known for a long time.

About twenty years ago, Ziegler-Heitbrock and his team identified the nonclassical monocytes. Only a low level of CD14 is expressed on their surface, but there is a high level of CD16. They increase mainly during inflammatory processes. The advantage of a uniform nomenclature is illustrated in these cells. They were previously categorized as CD16+ cells, proinflammatory monocytes, small, patrolling or Ly6Clow cells. Now they are only called nonclassical monocytes or CD14+CD16++ cells. The intermediate CD14++CD16++ monocytes in healthy people occur only in extremely low numbers. They become detectable only during inflammatory processes and after treatment with cytokines. The new classification was also adopted for the mouse model. However, other markers are used for their characterization.

Diagram of the New Populations of Leukocytes



The newly developed system for denoting white blood cells is based on the division into groups using a simple name, followed by informative markers.

They are subdivided into plasmacytoid and myeloid dendritic cells of the blood, and the names are combined with characteristic surface markers. The term blood in the name indicates that these are exclusively immature types of the dendritic cell lineage, circulating in the blood. According to this nomenclature, plasmacytoid CD303+ blood DCs denotes immature cells with the characteristics of circulating sentinel cells, which produce an especially large amount of interferon. Myeloid CD1c+ blood DCs und myeloid CD141+ blood DCs also denote cells with sentinel properties, but also show characteristics of both immature and precursor cells.

For mouse cells the scientists recommend an analogous subdivision of dendritic cells. However, reliable markers still have to be identified. The new uniform nomenclature can then easily be adapted to new findings. It enables clear scientific communication between researchers around the world.

White blood cells – leukocytes: As part of the immune system they defend the body against pathogens and foreign structures. They can also trigger autoimmune diseases. The leukocytes include various groups of monocytes, lymphocytes and granulocytes. In recent years, new subpopulations such as dendritic cells and CD16-positive monocytes have been detected.

Original Publication
Loems Ziegler-Heitbrock et al.: Nomenclature of monocytes and dendritic cells in blood.
Blood 116 (2010) 74-80 | doi:10.1182/blood-2010-02-258558

Proliferation Mechanism of Epstein-Barr Virus Elucidated

"Our activities bridge the gap from basic research and the biology of viral infections to the study of the immune response in people with infections. We want to understand what strategies herpes viruses have developed that make them so successful. However: All strategies have an Achilles heel. Our aim is to find this weak point in order to combat diseases related to these herpes viruses effectively."

Prof. Dr. Wolfgang Hammerschmidt

since 2008 Acting director of the Institute of Clinical Molecular Biology and Tumorgenetics — **2002** Aarson Award of the City of Berlin — **since 1998** Head of the Research Unit Gene Vectors at Helmholtz Zentrum München — **1996** Löffler-Frosch Prize of the German Association of Virology; Dr.-Emil-Salzer Prize of the State of Baden-Württemberg — **1990–1997** Group leader at Helmholtz Zentrum München — **1990** Habilitation in virology, Free University Berlin — **1989** Visiting assistant professor, McArdle Laboratory for Cancer Research, Madison, Wisconsin, USA — **1987–1988** McArdle Laboratory for Cancer Research, Madison, Wisconsin, USA, German Research Foundation fellowship — — **1984-1987** Postdoc at the Institute of Virology, Free University Berlin

Cooperation Partners / Authors

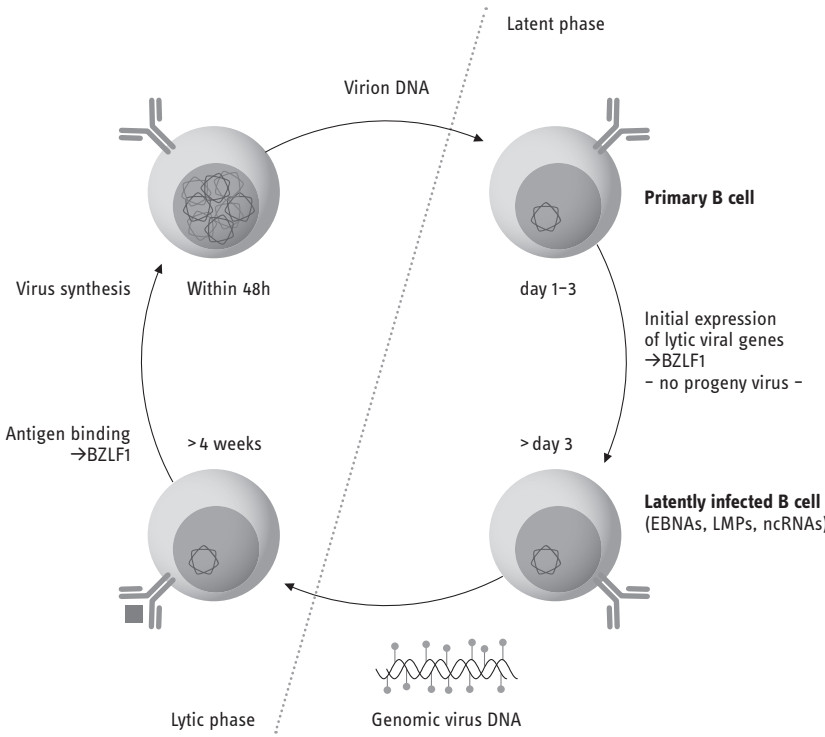
Helmholtz Zentrum München Markus Kalla, Anne Schmeinck, Martin Bergbauer, Dagmar Pich, Wolfgang Hammerschmidt

Scientists of Helmholtz Zentrum München have deciphered a key mechanism of the Epstein-Barr virus (EBV) proliferation. In a study led by Wolfgang Hammerschmidt, the researchers succeeded in elucidating the function of the viral BZLF1 protein which plays an important role in virus replication. Since Epstein-Barr viruses can cause certain forms of cancer, these findings are of great importance for understanding how EBV-induced tumors develop.

The Epstein-Barr virus, a virus of the herpes family, has two different life phases: Immediately after infection of the host cell, the virus first enters into the so-called latent phase, a kind of hibernation. Only a few EBV genes – the so-called latent genes – are active and ensure that the EBV genome remains stable in the nucleus of the infected cell, while the host cell replicates normally. Under certain circumstances, however, this peaceful coexistence ends, and the virus becomes active again and multiplies in the cell – the lytic phase – or induces unrestrained host cell division and thus the formation of tumors. Patients with a weakened or suppressed immune system are particularly vulnerable to EBV-induced tumor formation.

The causes for the transition of EBV from an inactive to an active state have thus far been unclear – especially the factors that are responsible for this and the molecular mechanisms that are involved. The researchers led by Wolfgang Hammerschmidt have now discovered how the virus can switch from the latent phase to the active phase. The BZLF1 protein reactivates the approximately 70 EBV genes that are important for virus replication. These EBV genes are silenced during the latent phase: Methyl groups bound to specific DNA segments prevent the production of the proteins.

EBV Has a Biphasic Life Cycle



The latent infection of human B cells, the host cell of EBV, is characterized by the proliferation of infected cells in the first phase. De novo viral synthesis takes place in the second, lytic phase, in which the host cell is reprogrammed and releases infectious viral particles. The temporal sequence of the two phases is regulated by a switch of the viral DNA by means of methyl groups, which the host cell induces only gradually.

The BZLF1 protein recognizes this methylation pattern on the DNA and can bind to it via its DNA-binding domain. Another domain of BZLF1 activates the silenced genes directly. Such a molecular mechanism was unknown until now: Researchers assumed that the methyl groups first have to be deleted from the DNA before the corresponding genes can be reactivated. The BZLF1 protein overcomes this hurdle.

These findings are important for two reasons: EBV serves as a model system for human herpes infections. Moreover, it can cause certain types of cancer – including lymphoma, cancers of the nose and throat as well as stomach cancer – which can now be better understood.

Over 90 percent of adults have evidence of previous infection with the Epstein-Barr virus (EBV), also called human herpesvirus 4 (HHV-4). EBV is a virus of the herpes family. Together with viruses of other families it is responsible for the development of about 15 percent of all cancer cases in humans. It can cause lymphoma, cancers of the nose and throat and stomach cancer, which mainly occur in immunosuppressed patients. The virus also serves as a model for other human herpes infections.

Original Publication

Markus Kalla et al.: AP-1 homolog BZLF1 of Epstein-Barr virus has two essential functions dependent on the epigenetic state of the viral genome. Proc. Natl. Acad. Sci. USA 107 (2010) 850-855 | doi:10.1073/pnas.0911948107

Highly Specific Antibodies Destroy Malignant Tumors

"In about two years we plan to begin with a first clinical study to examine the anti-tumor activity of cmHsp70.1 antibody. Another goal is to develop drug / radionuclide delivery systems based on cmHsp70.1 antibody. To achieve this we will produce antibody-drug conjugates that unfold their destructive effect within cancer cells."

Scientists of Helmholtz Zentrum München and Technische Universität München have developed a new tumor-specific antibody. This antibody enables the innate immune system to specifically target and recognize tumor cells and then to destroy them. Due to its high specificity, the antibody opens up an avenue for developing an effective and targeted tumor therapy with minimal side effects.

Prof. Dr. Gabriele Multhoff

since 2008 Partner in the EU integrated project CARDIORISK — **since 2007** Associate professor of Experimental Radiooncology and Radiation Biology in the Department of Radiation Therapy and Radiological Oncology, University Hospital rechts der Isar, Technische Universität München and head of the clinical cooperation group Innate Immunity in Tumor Biology, Helmholtz Zentrum München — **1999–2002** Group leader of the research group NK Cells at University Hospital Regensburg — **seit 1999** CEO of multimmune GmbH

Cooperation Partners / Authors

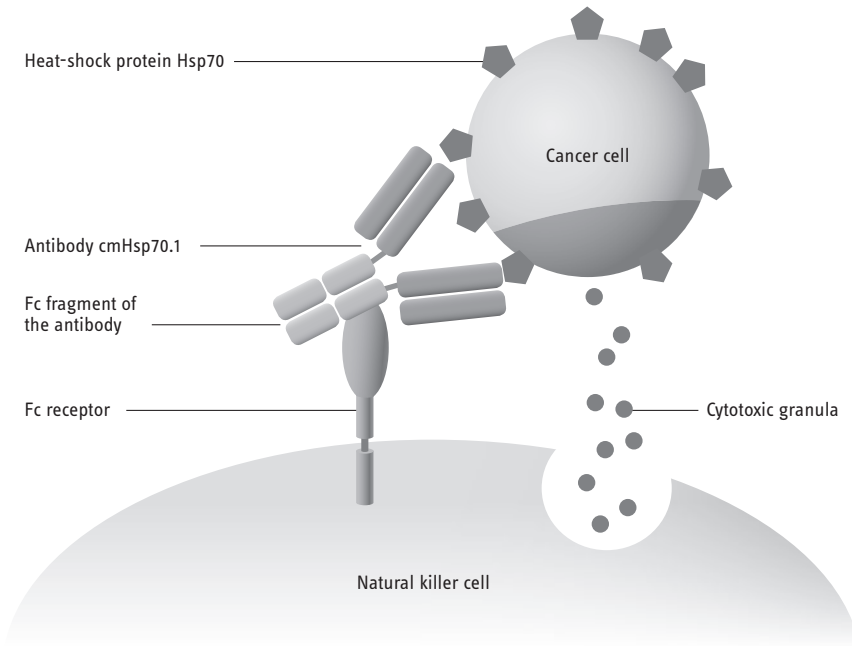
Helmholtz Zentrum and Technische Universität München Gabriele Multhoff, Stefan Stangl, Mathias Gehrmann, Julia Riegger, Kristin Kuhs, Isabelle Riederer, Wolfgang Sievert, Kathrin Hube — **Helmholtz Zentrum München** Ralph Mocikat, Elisabeth Kremmer — **Technische Universität München** Lars Friedrich, Arne Skerra — **University of Göttingen** Ralf Dressel — **University of Sheffield** Alan G. Pockley — **Hungarian Academy of Sciences, Szeged** Laszlo Vigh

The research group of Gabriele Multhoff developed the mouse monoclonal antibody (mAb) cmHsp70.1 that has a special property: It binds to heat-shock protein 70 (Hsp70), which is found only on the surface of malignant cells. This binding activates white blood cells, such as natural killer cells (NK cells) and macrophages, to mediate a specific killing of tumor cells.

Mice were injected with a peptide of Hsp70, termed TKD, and their immune system (B cells) produced the antibody cmHsp70.1. The target structure of cmHsp70.1 antibody, Hsp70, is located on the cell surface of numerous types of malignant tumors. These tumors are highly aggressive, grow rapidly and invasively and metastasize at an early stage.

After binding of the antibody to membrane-bound Hsp70 on tumors in mice, the innate immune system becomes activated and the malignant tumor is destroyed. The anti-tumor activity of cmHsp70.1 antibody can be promoted by the addition of interleukin-2. Interleukin-2 stimulates the growth of the innate immune cells and is already used in the treatment of malignant tumors.

Heat-Shock Protein Mediates Cell Toxicity



Cellular toxicity mediated by cmHsp70.1: The antibody cmHsp70.1 binds the heat-shock protein Hsp70 to the surface of the cancer cell. On the cell membranes of natural killer cells and macrophages are Fc receptors, which are deposited at a certain region of the antibody – the Fc fragment. As a result, the immune cells destroy the cancer cell.

It is very likely that cmHsp70.1 antibody is effective not only in mouse tumors, but also in human malignancies. The researchers showed that the antibody cmHsp70.1 binds to a number of human tumors such as colorectal, pancreas, breast and lung tumors, malignant melanomas and to leukemia and lymphoma.

In contrast to previous immune-stimulating therapies for cancer, the new antibody is characterized by its high specificity. It exclusively destroys malignant cells while sparing normal cells. Thus, cmHsp70.1 offers the possibility of successfully treating aggressive forms of cancer with minimal side effects.

Heat-shock proteins are expressed when cells are exposed to elevated temperatures or other stress factors. They also play an important role in protein folding and stabilization of proteins under physiological conditions. According to their molecular weights heat-shock proteins are classified in different families. Intracellularly, Hsp70 can protect tumor cells against programmed cell death. Highly aggressive tumors and metastases express Hsp70 on their cell surface and thus Hsp70 serves as a tumor specific target structure.

Original Publication

Stefan Stangl et al.: Targeting membrane heat-shock protein 70 (Hsp70) on tumors by cmHsp70.1 antibody. PNAS Early Edition (2010) | doi:10.1073/pnas.1016065108

Structural Details of a Cellular Signaling Protein Determined

"Using methods of structural biology, we can describe the molecular mechanisms of biological processes at atomic resolution. We want to use the obtained information to develop new bioactive small molecules as inhibitors of proteins. These molecules shall enable us to better understand cellular processes and also represent a starting point for the development of new drugs to treat diseases."

Dr. N. Helge Meyer
2006–2011 Doctoral student at the Institute of Structural Biology, Helmholtz Zentrum München and Technische Universität München

Prof. Dr. Michael Sattler
since 2007 Director of the Institute of Structural Biology at Helmholtz Zentrum München and professor of Biomolecular NMR Spectroscopy at Technische Universität München — **1997–2006** Group leader of the research group Biomolecular NMR Spectroscopy at the European Molecular Biology Laboratory (EMBL), Heidelberg — **1995–1997** Postdoc Abbott Laboratories, Abbott Park / Chicago, USA

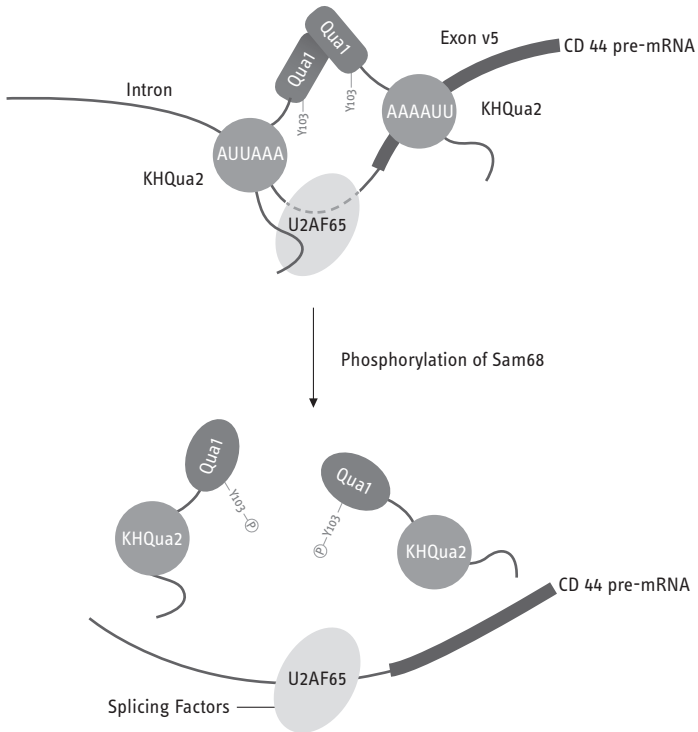
Prof. Dr. Ruth Brack-Werner
since 2009 Deputy director of the Institute of Virology, Helmholtz Zentrum München — **2006–2007** Acting director of the Institute of Molecular Virology — **since 2007** Associate professor at Ludwig-Maximilians-Universität Munich — **since 1990** Group leader of the research group Retrovirus-Cell Interactions — **1983–1989** Postdoc, Technische Universität München and Institute of Pathology

Cooperation Partners / Authors
Helmholtz Zentrum München und Technische Universität München N. Helge Meyer, Konstantinos Tripsianes, Tobias Madl, Fatiha Kateb — **Technische Universität München** Michelle Vincendeau — **Helmholtz Zentrum München** Ruth Brack-Werner, Michael Sattler

Scientists at Helmholtz Zentrum München and Technische Universität München have succeeded in solving the structure of an important region of the Sam68 protein. Among other functions, Sam68 regulates specific processes in the cell cycle and in apoptosis – programmed cell death – and plays an important role in cancer development.

The Sam68 protein (Src-associated during mitosis, 68 kDa Protein) is a prototypical member of the STAR protein family (STAR: signal transducer and activator of RNA). STAR proteins bind to messenger RNA (mRNA), and upon reception of external signals, they influence certain cellular processes as the regulation of the cell cycle or tissue development. Sam68 modulates the alternative splicing of CD44 and Bcl-xL. Both proteins are involved in apoptosis; malfunctions may promote tumor growth. Sam68 and other STAR proteins recognize bipartite RNA sequences and are thought to function as homodimers, i.e. an aggregate of two identical subunits. However, the structural details and the functional roles of this dimerization have remained elusive until now.

Model of the Function of Sam68 in Alternative mRNA Splicing



Model of Sam68 interaction: Dimerization of Sam68 by Qua1 domain mediates alternative splicing of the proteins CD44 and Bcl-xl.

Using NMR spectroscopy, Michael Sattler and his team determined the spatial structure of the Qua1 domain of Sam68. The Qua1 domain is responsible for dimerization of the protein. Together with the research group led by Ruth Brack-Werner of the Institute of Virology, the scientists showed that this part of the protein is essential for the biological function of Sam68. The three-dimensional structure characterized in this study adopts an unusual fold, in which the two Qua1 domains interact and mediate the dimerization of Sam68. Each of the Qua1 monomers consists of two antiparallel α-helices that are perpendicular to each other in the dimer. Mutation analyses of Sam68 in vitro and in a cellular test system showed that specific amino acids that are essential for dimerization of the Qua1 domain are also important to ensure that the Sam68 protein can modulate alternative splicing of the pre-mRNA molecules.

Elucidating the structure of the Qua1 represents an important contribution to understanding the molecular mechanisms of Sam68 function – and forms the basis for illuminating the role of the protein in the development of cancer and other diseases.

Alternative splicing is a process which takes place during transcription in the protein synthesis of eukaryotes. Several different messenger RNA (mRNA) variants are generated from a common pre-mRNA molecule, subsequently forming different proteins. In humans, the majority of genes appear to be alternatively spliced. Mis-regulated alternative splicing is one of the key factors in the development of cancer.

Original Publication
N. Helge Meyer et al.: Structural basis for homodimerization of the Src-associated during mitosis, 68 kDa-protein (Sam68) Qua1 domain. J. Biol. Chem. 285 (2010) 28893-28901 | doi:10.1074/jbc.M110.126185

Molecular Markers Enable Earlier Prognosis for Osteosarcoma Patients

"We seek to identify genetic mutations that can be used as prognostic markers or therapeutic target structures. Using these, new therapeutic strategies can be developed for patients with a poor prognosis. These are patients who have metastases, who respond poorly to chemotherapy or who suffer a relapse."

A new test system helps physicians predict the survival chances of patients with osteosarcoma already at the time of diagnosis. For this purpose structural aberrations in the chromosomes and allelic imbalances are analyzed.

Dr. Michaela Nathrath

since 2008 Director of the Department of Pediatric Hematology and Oncology at Klinikum Kassel, Federal Cross of Merit with ribbon — **since 2005** Head of the clinical cooperation group Osteosarcoma at Helmholtz Zentrum München— **2003–2008** Executive senior physician of Pediatric Hematology / -Oncology, physician in charge of the Department of Pediatrics of Technische Universität München, Habilitation — **1998–2001** Habilitation scholarship Helmholtz Zentrum München— **1991–1998** Specialist training, Children's Hospital of Technische Universität München, Specialist in pediatric and adolescent medicine — **1989–1990** Research assistant, University College Hospital London — **1988–1989** Research associate at the Institute of Pathology of Ludwig-Maximilians-Universität Munich

Cooperation Partners / Authors

Helmholtz Zentrum München Michael Rosemann, Axel Walch, Michael J. Atkinson — **Helmholtz Zentrum München and Technische Universität München** Jan Smida, Michaela Nathrath — **Helmholtz Zentrum München and University Hospital Basel** Daniel Baumhoer — **Technische Universität München** Stefan Burdach — **University Hospital Basel** Gernot Jundt — **Klinikum Stuttgart** Stefan Bielack — **Heinrich Heine University Düsseldorf** Christopher Poremba — **Saarland University** Klaus Remberger — **University of Münster** Eberhard Korsching — **Knopf'sche Kinderklinik, Nuremberg** Wolfram Scheurlen — **University of Giessen** Christian Dierkes

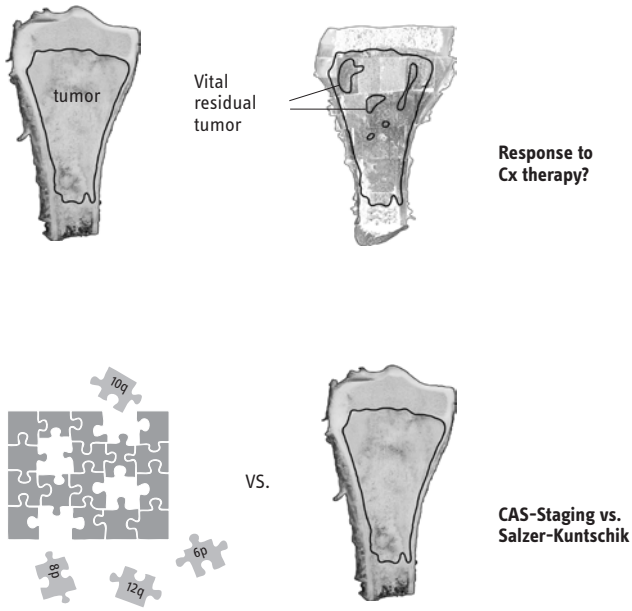
Up to now, the clinical course of patients with osteosarcoma could not be predicted until after neoadjuvant therapy. The extent of the tumor necrosis had to be determined histologically. To find a reliable molecular marker, the research group led by Michaela Nathrath at Helmholtz Zentrum München and the Department of Pediatrics of Technische Universität München analyzed samples of 45 osteosarcoma patients before starting treatment. The bone tumors were characterized by complex karyotypes with a high frequency of chromosomal copy number changes. Using single nucleotide polymorphism (SNP) arrays, the scientists searched for numeric aberrations and allelic imbalances in the genome.

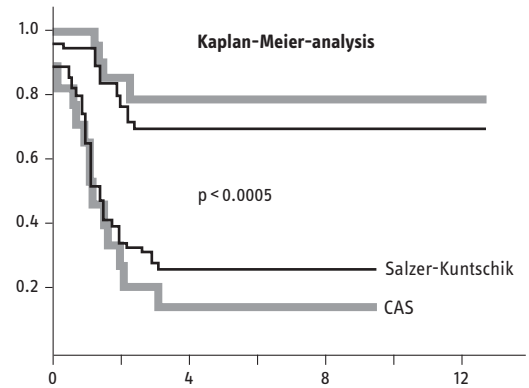
The study revealed that specific chromosomal regions are often copied several times. Another region was no longer present on both chromosomes in nearly half of the samples (LOH; loss of heterozygosity). The absolute number of LOHs in the genome was correlated with poor patient prognosis. If the number of LOHs in the patients was high, they had a significantly poorer response to therapy than patients with a low number of LOHs. The prognostic value depended on the chromosomal region where the SNPs were located.

From the genomic alterations, the scientists developed a chromosomal staging system (CAS) with which the patients' prognosis can be predicted very reliably. In direct comparison, it is significantly superior to conventional regression grading, in which the success of chemotherapy is measured solely on morphological changes.

The determination of chromosomal aberrations could be a reliable marker for predicting the course of the disease in osteosarcoma patients and their response to neoadjuvant therapy. Patients who respond poorly to the usual neoadjuvant therapies would be identified before starting treatment – the doctors could adjust the

Chromosomal Aberrations as Prognostic Markers





Molecular markers in osteosarcoma patients: Both the absolute number of LOHs (loss of heterozygosity) in the genome and the number of alterations were significantly correlated with poor patient prognosis.

individual therapy right from the beginning. At present a prospective validation is being undertaken to verify the reliability of the proposed CAS system. The goal is to establish the future role of the new staging system in routine diagnosis and potentially also in the therapeutic stratification of the patients.

Osteosarcomas are highly malignant primary bone tumors, most commonly found in children and adolescents between ten and 20 years. The disease is fatal for about one-third of those affected, despite intensive treatment. To date, there are no reliable molecular markers which can be used to estimate the prognosis of the patients.

Original Publication
Jan Smida et al.: Genomic alterations and allelic imbalances are strong prognostic predictors in osteosarcoma. Clin Cancer Res 16 (2010) 4256-4267 | doi:10.1158/1078-0432.CCR-10-0284

Nitric Oxide Is the Key to Plant Immunity

"A better understanding of plant defense mechanisms could enable us to specifically strengthen the immune system of plants in the future. This seems to be a promising approach to reduce the use of chemical pesticides. The result would be less contamination in soils and healthier foods."

Dr. Christian Lindermayr
since 2008 Group leader of the research group Redox Signaling and Proteomics in the Institute of Biochemical Plant Pathology, Helmholtz Zentrum München — **2002–2008** Research associate, Institute of Biochemical Plant Pathology — **1998–2002** PhD, Ludwig-Maximilians-Universität Munich

Prof. Dr. Jörg Durner
since 2009 Chair of Biochemical Plant Pathology, Technische Universität München — **since 2008** Director of the Institute of Biochemical Plant Pathology, Helmholtz Zentrum München — **since 1999** Group leader of the research group Redox Signaling and Proteomics — **1999** Habilitation, University of Konstanz — **1994–1998** Research associate, Waksman Institute, Rutgers University, USA — **1991–1994** Postdoc, Department of Physiology and Biochemistry of Plants, University of Konstanz

Cooperation Partners / Authors
Helmholtz Zentrum München Christian Lindermayr, Simone Sell — **Helmholtz Zentrum München and Technische Universität München** Jörg Durner — **Ludwig-Maximilians-Universität Munich** Bernd Müller, Dario Leister

Scientists of the Institute of Biochemical Plant Pathology have shown that nitric oxide also plays a crucial role in plants with respect to defense against pathogens. Apparently, redox processes take place that are very similar to those in mammals. The study contributes to the understanding of the basic principles of plant defense mechanisms and could lead to new approaches in plant protection.

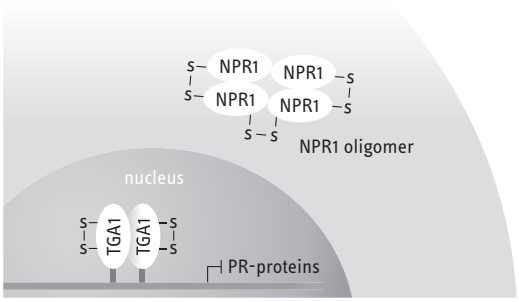
Nitric oxide is indispensable for mammal metabolism: The inter- and intracellular messenger substance is involved in numerous cellular functions, including the defense against pathogens. If nitric oxide reacts with the redox centers of specific proteins, important signals are activated that set the immune system in motion.

Like humans and animals, plants can develop a systemic resistance against pathogens. Scientists have assumed for several years that nitric oxide contributes in an essential way to these "acquired" immune processes. Researchers led by Christian Lindermayr and Jörg Durner of the Institute of Biochemical Plant Pathology of Helmholtz Zentrum München have now shown on the crucifer Arabidopsis thaliana how nitric oxide initiates the cascade of plant defense.

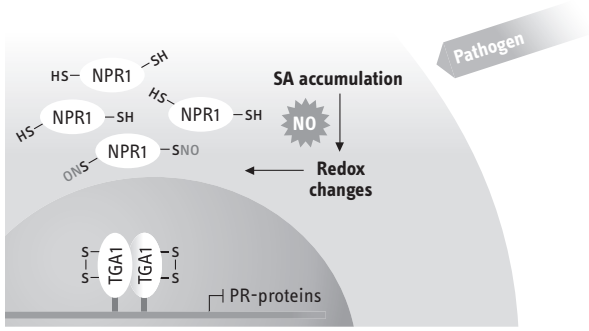
The molecular switch for the plant immune system is the protein NPR1 (non-expressor of pathogenesis-related genes 1). In the inactive state it is present in the cell as an oligomer. If the plant is infested by pathogens, NPR1 is reduced to its monomeric, reactive form. The monomers migrate to the nucleus where they interact with the transcription factor TGA1 and initiate the expression of the necessary defense genes. Nitric oxide is evidently an important redox regulator for the NPR1 / TGA1 control system: By means of S-nitrosylation of NPR1 and TGA1 it generates important signals to trigger this defense mechanism.

Activation of Pathogen Defense in Plants by Nitric Oxide

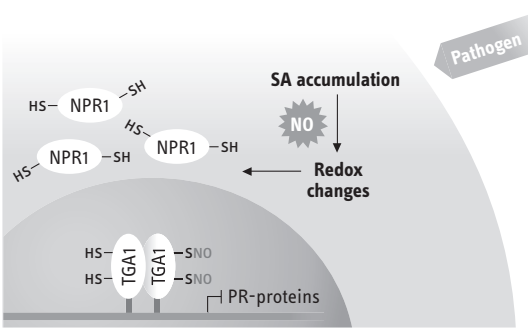
Nitric oxide reacts with the redox centers of the proteins NPR1 and TGA1 and thus initiates the defense cascade of the plant cell.



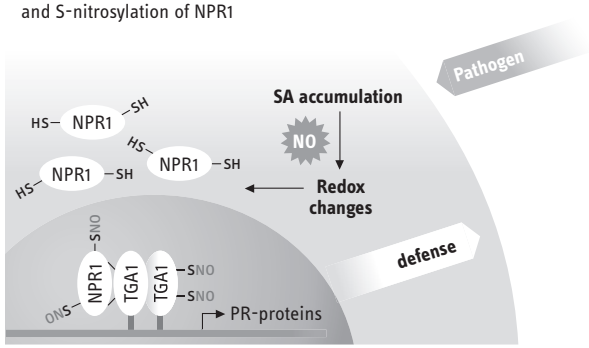
Noninfected plant cell



1. Infection leads to the production of nitric oxide, monomerization and S-nitrosylation of NPR1



2. S-nitrosylated NPR1 is transferred into the nucleus, TGA1 is S-nitrosylated



3. Reaction of NPR1 and TGA1 causes expression of defense genes

The findings provide basic knowledge about plant immune defense, out of which new and sustainable approaches in plant protection may be developed over the long term. Here the focus would be on a targeted strengthening of the plant's immune system. In addition, the results contribute to a deeper understanding of the complex redox regulation. In animal and plant organisms, redox reactions not only play a role in disease resistance but also in reactions to stress and cell death.

Similar to humans and animals, plants have an innate immunity. Defensive strategies include the selective production of nitric oxide and reactive oxygen, the expression of defense genes and the initiation of programmed cell death. In the course of their lifetime plants develop systemic resistance mechanisms against a broad spectrum of plant pathogens (fungi, bacteria and viruses).

Original Publication

Christian Lindermayr et al.: Redox regulation of the NRPR1-TGA1system of Arabidopsis thaliana by nitric oxide. The Plant Cell, 22 (2010) 2894–2907 | doi:10.1105/tpc.109.066464

Dr. Daniel Razansky

Using photoacoustic signals, Dr. Daniel Razansky observes biological processes live. The sound of light, which interacts with molecular biomarkers in deep tissue layers, makes these visible. The European Research Council selected Razansky's work for a Starting Grant in 2010. This will provide him with approximately 1.6 million euros for the application of the multispectral optoacoustic tomography (MSOT), co-developed by him, to biomedical questions. Razansky aims to use his method to depict neurological processes and cardiovascular mechanisms in the living organism – in real time.

Working Group Head and deputy director of the Institute of Biological and Medical Imaging at Helmholtz Zentrum München — **since 2008** lecturer of biological imaging at Technische Universität München — **2006** Ph.D. in biomedical engineering — **2006–2007** Research Fellow, Center for Molecular Imaging Research at Harvard Medical School and at the Massachusetts General Hospital in Boston — Degree in electrical engineering at the Technion – Israel Institute of Technology in Haifa — Born **1974** in St. Petersburg

2010 Biovaria Spin-off Award — **2008** Biomedical Innovation Award of the Federal Ministry of Education and Research — **2005** Biovision World Life Sciences Fellow

The Sound of Light

Starting Grant from the
European Research Council for
Daniel Razansky

“The sound of light will give us insight into physiological and pathophysiological processes. Using high-resolution optoacoustic procedures, we will have a completely new tool to continuously observe life processes. This will render not just new biological and medical development processes possible, but also practical applications in order to observe diseases like cancer, neurological disorders and inflammatory processes in living organisms.”

Cardiovascular Research

at Helmholtz Zentrum München since 1960

1984
The MONICA myocardial infarction registry is established in Augsburg

1986
Researchers at the Center develop a marketable version of one of the world's first mobile systems for automatic ECG analysis

1980
The Institute of Medical Informatics and Systems Research researches social variables and cardiovascular risk factors as part of the Munich Blood Pressure Study

1985
The Lübeck Blood Pressure Study provides comparative reference data for the first Munich Blood Pressure Study

1995
The MONICA project is completed – the myocardial infarction registry is continued

1969
The newly established research group Data Processing in Medical Diagnostics analyzes possibilities for an automated EEG analysis

1985
In Augsburg the studies conducted for the international study "Monitoring of Trends and Determinants of Cardiovascular Disease" (MONICA) by the World Health Organization (WHO) begin

The Future

By combining epidemiology, genetics, and biomelecular research, the Center contributes to the elucidation of causes and risk factors of cardiovascular diseases

2010

Helmholtz Zentrum München becomes a partner of the German Centre for Cardiovascular Research (DZHK)

2010

In a meta analysis of genome-wide association studies, 95 new gene loci of the lipid metabolism are identified

2009

Researchers at the Center identify genetic risk factors for sudden cardiac death

2004

Survey results of the Center prove for the first time a connection between exposure to fine particles and the risk of myocardial infarction

2002

The Center begins its data collection for a study on the genetics of cardiac arrhythmia

2008

KORA-AGE takes up research into myocardial infarctions, strokes, and diabetes in old age

1996

Based on MONICA, studies in Cooperative Health Research (KORA) begin in Augsburg

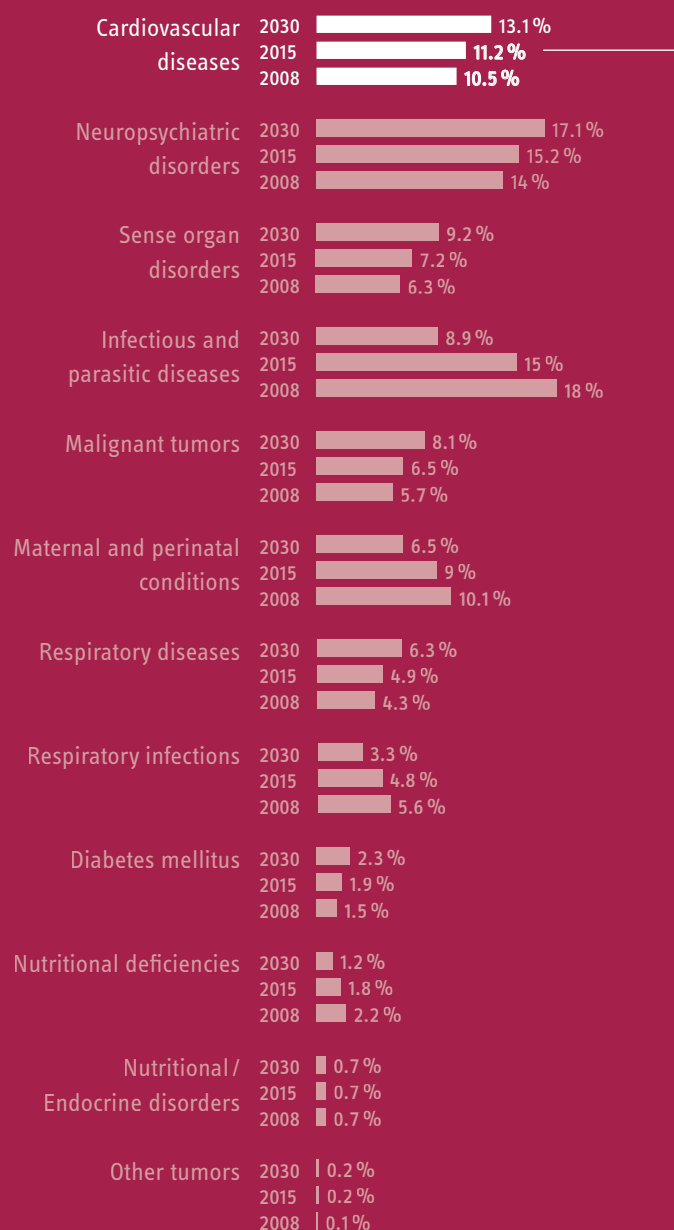
1997

The surveys for genetic determinants of coronary heart diseases are completed

Partner of the German Centre for Cardiovascular Research (DZHK)

Helmholtz Zentrum München

Causes of the Global Burden of Disease: Cardiovascular Diseases Remain at a High Level



	2008	2015	2030
Rheumatic heart disease	0.3 %	0.3 %	0.3 %
Hypertensive heart disease	0.6 %	0.6 %	0.8 %
Ischemic heart disease	4.4 %	4.7 %	5.5 %
Cerebrovascular diseases (e.g. stroke)	3.3 %	3.5 %	4.3 %
Inflammatory heart disease	0.4 %	0.4 %	0.4 %

These projections show the share of the overall burden of disease in percent, stated in DALYs.

One DALY (Disability Adjusted Life Year) is a year of healthy life lost to disability. The "DALY" figure aims to not just summarize the mortality, but also the impairment of the normal life, free of complaints, through an illness, by providing a comparable measure.

Source: Projections of mortality and burden of disease, world health organisation, baseline scenarios 2008, 2015, 2030
www.who.int/healthinfo/global_burden_disease/projections/en/index.html

The **German Centre for Cardiovascular Research** is being established by the Federal Ministry of Education and Research as part of a competition for setting up the German Centres for Health Research. Helmholtz Zentrum München is involved in this centre through the Munich Heart Alliance founded in 2010. This science network pools the competencies of both Munich universities, the Max Planck Institute of Biochemistry, and Helmholtz Zentrum München in order to boost in particular the translation of insights from basic research into clinical research and application.

"As a partner of the German Centre for Cardiovascular Research, we aim to successfully combat cardiovascular diseases. Our research focuses in particular on the analysis of genetic factors and their interaction with environmental influences and lifestyle. By using our expertise from large population surveys, we contribute to cause studies. Thus, research in networks lays the foundations for developing new approaches for the prevention, early detection and treatment of the most frequent cause of death in Western society."

Prof. Dr. Annette Peters is Director of the Institute of Epidemiology II and lectures as Adjunct Associate Professor for Environmental Health at Harvard Medical School in Boston.

Prof. Dr. Thomas Meitinger is Director of the Institute of Human Genetics at Helmholtz Zentrum München and Chair of Human Genetics at Technische Universität München. Together they coordinate the Center's contributions for the Munich Heart Alliance.

Toward a Better Understanding of Lipid Metabolism

"The more we know about lipid metabolism, the better we can develop targeted therapies. And when we know more about the influence of genetic variants on the concentration of lipids in the blood, we can identify individuals who are at risk and for whom specific changes in their diet and increased physical activity are especially important."

Angela Döring
1980 to the present Research associate at the Institute of Epidemiology, Helmholtz Zentrum München — **1998–2008** Lecturer at Ludwig Maximilians-Universität Munich

Dr. Christian Gieger
2010 Paula and Richard von Hertwig Award for Interdisciplinary Cooperation — **since 2009** Group leader of the research group Genetic Epidemiolog — **since 2004** Research associate at Helmholtz Zentrum München and at Ludwig-Maximilians-Universität Munich — **1999–2004** Researcher in industry and at the Fraunhofer Institute St. Augustin

Prof. Dr. Thomas Meitinger
since 2000 Director of the Institute of Human Genetics, Helmholtz Zentrum München and Technische Universität München — **until 2000** Head of the Molecular Genetics Lab, Children's Hospital, Ludwig-Maximilians-Universität Munich — **until 1988** German Research Foundation fellow at the University of Oxford — **until 1985** Resident physician, Clinic of Pediatric Surgery, Karlsruhe

Prof. Dr. Dr. H.-Erich Wichmann
since 1990 Director of the Institute of Epidemiology and since 1995 chair of Epidemiology, Ludwig-Maximilians-Universität München — **1988–1995** Head of the Department of Occupational Safety and Environmental Medicine, University of Wuppertal — **1983–1988** Head of the Biostatistics Department, Medical Institute of Environmental Hygiene, Düsseldorf

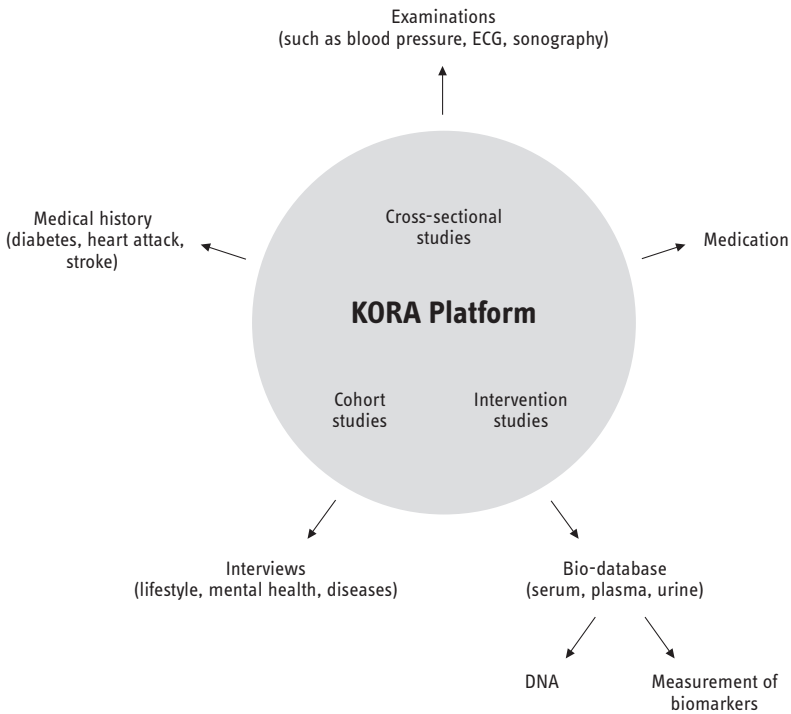
Cooperation Partners / Authors
211 international scientists from 117 institutions
Helmholtz Zentrum München H. Erich Wichmann, Iris M. Heid, Christian Gieger, Angela Döring, Thomas Meitinger

Through a meta-analysis of genome-wide association studies, 95 loci associated with lipid metabolism were identified and characterized, 59 of which were previously unknown. The results shed light on the lipid metabolism and the causes of coronary heart disease.

The concentration of blood lipid levels is inherited to a considerable extent. Blood lipid levels are considered to be an important risk factor of coronary heart disease. It is therefore particularly interesting to know which loci in the genome are responsible for the expression of the different lipids. To find this out, the research group led by H.-Erich Wichmann, together with colleagues around the world, analyzed 46 studies. The researchers from Helmholtz Zentrum München participated with their data from the KORA study. KORA stands for Cooperative Health Research in the Region of Augsburg.

The genome-wide association studies were based on the data of more than 100000 individuals of European ancestry. A total of 2.6 million single nucleotide polymorphisms (SNPs), i.e. gene segments with single-base-pair differences, were tested to determine whether they influence the plasma concentration of individual lipid types. The researchers found 95 gene loci that were associated with at least one of the tested lipid types. Of these, 59 loci were previously unknown. Some of the newly discovered gene loci are located near previously identified regulators of lipid metabolism. But the analysis also revealed loci that were not previously associated with lipid metabolism. For three of the new genes the association to the lipid metabolism was already confirmed in a mouse model.

Data Collection in the KORA Studies



Comprehensive health parameters are collected within the scope of the KORA studies. The anonymized data are a valuable basis for investigating genetic risk factors.

In a further part of the study, the researchers investigated whether the loci found only in people of European ancestry also have an impact on the lipid traits of Asian or African populations. The results showed that most of the SNPs influence the lipid traits in the same way in all populations.

But are the SNPs also involved in the development of cardiovascular disease? To date, scientists have only been able to partly answer this question. Some of the recently found variants in the genome also show a correlation with blood lipid levels and with cardiovascular disease. It is still not completely clear what practical value can be gained from the analysis of genome-wide association studies. The results of this meta-analysis add to our fundamental understanding of lipid metabolism. They show how many different genes impact the concentration of blood lipid levels and the development of cardiovascular disease.

Elevated levels of blood lipids – cholesterol, low density lipoprotein (LDL) and triglycerides – and decreased high density lipoprotein (HDL) levels are risk factors in the development of cardiovascular disease and metabolic disorders such as diabetes. Scientists are seeking to develop therapies to better restore and maintain a healthy balance of blood lipid levels.

Original Publication

Tanya M. Teslovich et al.: Biological, clinical and population relevance of 95 loci for blood lipids. Nature 466 (2010) 707-712 | doi:10.1038/nature09270

Foundations of Life

Gene Targeting by Homologous Recombination in Mammalian Genomes

"By inducing mutagenesis in the mouse genome directly in the mouse zygotes, researchers no longer need to go through the complicated process of culturing embryonic stem cells and producing chimeras. Mouse models of human diseases can be developed faster and more flexibly, enabling the study of the role of the involved genes. For medical research and biotechnology purposes, genetic animal models are thus possible using other mammalian species such as rats, pigs or cows."

Dr. Ralf Kühn
since 2002 Institute of Developmental Genetics, Helmholtz Zentrum München, research team leader — **until 2002** Head of Mouse Genetics at Artemis Pharmaceuticals GmbH, Cologne — **until 1998** Postdoc and research assistant (from 1994), Institute of Genetics, University of Cologne

Prof. Dr. Wolfgang Wurst
since 2002 Director of the Institute of Developmental Genetics, Helmholtz Zentrum München and Technische Universität München — **since 1997** Group leader of the research group Molecular Neurogenetics, Max Planck Institute of Psychiatry, Munich — **until 1997** Group leader of junior research group, GSF-National Research Center for Environment and Health, Institute of Mammalian Genetics — **until 1994** Postdoc and research associate — **from 1991** at the Samuel Lunenfeld Research Institute, Toronto, Canada — **until 1989** Postdoc, University of Göttingen

Cooperation Partners / Authors
Helmholtz Zentrum München und Technische Universität München Melanie Meyer, Martin Hrabě de Angelis, Wolfgang Wurst, Ralf Kühn — **German Centre for Neurodegenerative Diseases** Wolfgang Wurst

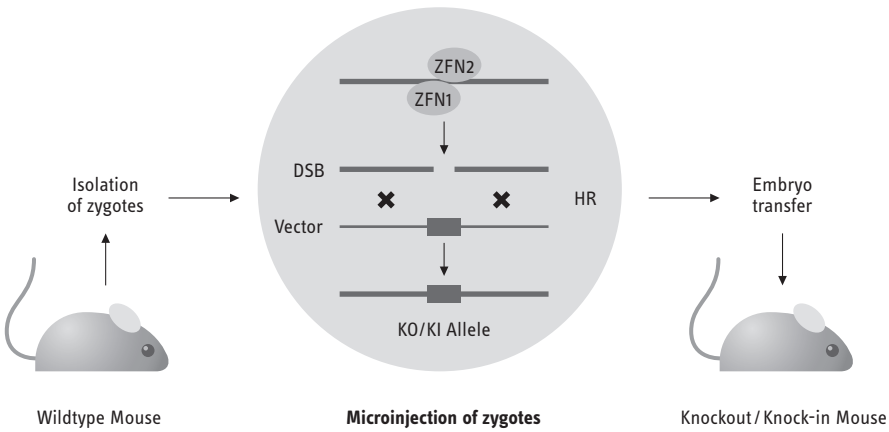
Researchers at Helmholtz Zentrum München have succeeded in modifying selected genes in mouse embryos. Using the new method, mutations are established in a single step without having to use ES cells. This method of inducing gene mutations in mammals saves time and has universal uses.

To obtain a detailed understanding of the function of genes in mammals, scientists primarily rely on the mouse model system. One of its uses is to characterize in detail genetically caused human diseases – that is, diseases that are based on errors in the DNA. An already long established research method in the mouse model is gene targeting, i.e. targeted gene modification. However, the current methods for generating such modifications of individual genes are very labor intensive and time consuming: Mutations are generated in isolated mouse embryonic stem cells, and these are subsequently established in chimeras and then in embryos. Only after this process has been completed can the effect of a modification in a specific gene be determined. The efficiency of mutations induced in this way is usually very slight.

The team led by Wolfgang Wurst and Ralf Kühn has developed a method with which the mouse genomes can be modified faster and more efficiently. The researchers found a way to make targeted gene mutations in mouse zygotes by injecting zinc-finger nucleases – in a single step without having to use ES cells.

Zinc-finger nucleases are artificial enzymes which can be engineered to cleave a specific sequence of the genomic double-strand DNA. If the mRNA for such an enzyme is microinjected into the mouse zygote in combination with an modified gene fragment containing e.g. a base substitution, an insertion, deletion or an additional new gene, the nuclease temporarily formed by the mRNA cleaves the genomic DNA at a defined site. At the site of this break the cell's own repair system fuses the new modified gene fragment into the DNA via homologous recombination.

Targeted Homologous Recombination of Mouse Genes



Zinc-finger nucleases (ZFN) cleave genomic DNA at a defined site. Repair enzymes fuse a copy of the vector gene into the double-strand break site. Viable mice with targeted, recombinant genes develop from these one-cell mouse embryos.

This is done – as the researchers have found in their experiments – with a frequency of 1.7 to 4.5 percent. Using this method, they have already generated several viable mice cultured with different, specifically targeted recombinant genes.

The new method offers an enormous time-saving potential; it is exponentially more efficient than previous methods and can be applied to other mammals. In the long term it is conceivable that not only supplementary genes can be introduced in this way, but also defective gene sequences can be replaced with healthy ones.

Zinc-finger nucleases bind to specific sequences of double-stranded DNA and break up the two strands with their nuclease subunits. The repair machinery of the cell copies similar sequences elsewhere in the genome and fuses them at the cleavage site. If a DNA sequence similar to the deleted sequence but containing an additional gene is inserted into the cell at the same time with the zinc-finger nuclease, the molecular machinery inserts the foreign gene construct during the repair.

Original Publication
Melanie Meyer et al.: Gene targeting by homologous recombination in mouse zygotes mediated by zinc-finger nucleases. PNAS 107(2010) 15022-15026 | doi / 10.1073 / pnas.1009424107

Combined Measurement of Radiation Dose and Biological Parameters

"Our biosensor has great potential for determining cellular activity and characterizing cell signaling processes. In addition to applications in medical technology, it could be used for new procedures in radiation therapy. Furthermore, the sensor can serve as a universal real-time dosimeter in critical environmental conditions."

PD Stefan Thalhammer

2009 Habilitation in physics, University of Augsburg — **since 2006** Group leader of the research group Radiation Biophysics, Institute of Radiation Protection, Helmholtz Zentrum München — **2001–2006** Postdoc in Geo- and Environmental Sciences, Ludwig-Maximilians- Universität Munich

Markus Hofstetter

since 2009 Doctoral studies, University of Augsburg and guest scientist, Helmholtz Zentrum München — **2008–2009** Research associate, Helmholtz Zentrum München — **until 2008** Undergraduate studies in Physics, Technische Universität München, and training in Industrial Electronics

Cooperation Partners / Authors

Helmholtz Zentrum München Markus Hofstetter, Maren Funk, Herwig G. Paretzke, Stefan Thalhammer — **Technische Universität München** John Howgate, Ian D. Sharp, Martin Stutzmann

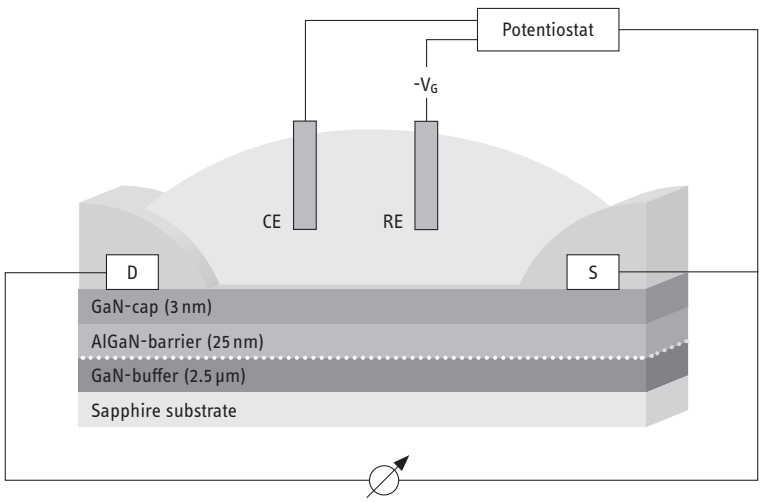
Scientists at the Institute of Radiation Protection have developed a biosensor that can measure pH value and radiation dose simultaneously. The device provides stable and reproducible readings for both parameters and works reliably even under critical conditions. As in vivo measuring device, the sensor could enable new applications in radiology and radiation biophysics in the future.

The influence of ionizing radiation on the organism is a high-priority research topic of scientists in the two fields of biological and medical research: A key issue is to determine the radiation threshold that marks the limit between reversible and irreversible damage to the organism. However, devices are not yet available which also measure the effects on biological systems in addition to intensity and wavelength of the radiation dose.

Scientists in the team of Stefan Thalhammer and Markus Hofstetter of the Institute of Radiation Protection have developed a biocompatible semiconductor sensor capable of simultaneous high-resolution pH measurements and also radiation detection and assessment in real time, providing stable and reproducible output signals for both parameters. The sensor reacts both during and after x-ray irradiation to both parameters and ensures that they are not mutually disruptive. Due to this dual sensitivity, the device enables multiparameter analyses of ion changes, for example in cell media.

The device consists of an AlGaN / GaN high electron mobility transistor and an additional GaN capping layer. This allows operation in aqueous solutions and in harsh environments – such as those found in the human body. Due to its robustness, its small size of less than one square millimeter and its almost energy self-sufficient operation, the sensor is well-suited for both medical radiation dosimetry and biosensing applications.

Real-Time Biosensor and Radiation Detector



Schematic layout of the AlGaN / GaN high electron mobility transistor (HEMT) for simultaneous measurement of radiation dose and pH value.

The use of the sensor in vivo could enable new applications both in radiology and in radiation biophysics. The sensor detects even the slightest radiation effects: It achieves highly accurate results even into the very low dose range (down to ~10 µGy). In contrast, conventional MOSFET-based radiation detectors, such as are now used in radiology, reach their detection limit in the low mGy region. In the future, scientists hope that experimental, diagnostic and therapeutic procedures can be improved and adapted on the basis of these expanded analysis capabilities.

Our organism is constantly exposed to ionizing radiation: Natural sources are mainly radon from the soil and cosmic radiation from outer space. Diagnostic x-ray and nuclear medicine methods contribute at least as much to the average radiation exposure of the population. Ionizing radiation damages the genetic material of cells, which – depending on the radiation dose – can lead to an increased risk of cancer or acute tissue damage.

Original Publication

Markus Hofstetter et al.: Real-time x-ray response of biocompatible solution gate AlGaN/GaN high electron mobility transistor devices. Applied Physics Letters 96 (2010) 092110 | doi:10.1063/1.3334682

Genome of a Model Grass Decoded

"The deciphering of the genomes of plants helps sustain and improve human food resources. With this knowledge, the breeding of cereal varieties can be specifically adapted to changing environmental conditions, thus enabling increased food security."

An international consortium has decoded the genome of the plant Brachypodium distachyon. Due to its close relationship with major food and pooid grasses such as wheat, barley and rye, this grass is of great scientific interest. A research group led by Klaus Mayer at the Institute of Bioinformatics and Systems Biology at Helmholtz Zentrum München was significantly involved in the sequencing of the genome.

Dr. Klaus Mayer

since 1999 Group leader of the research group Plant Genome Analysis at the Institute of Bioinformatics and Systems Biology, Helmholtz Zentrum München — **1997–1999** Research associate at the Martinsried Institute for Protein Sequences (MIPS), Max Planck Institute of Biochemistry, Munich — **1997** PhD in Developmental Biology — **1993–1997** — Research assistant at the Ludwig-Maximilians-Universität Munich and the University of Tübingen

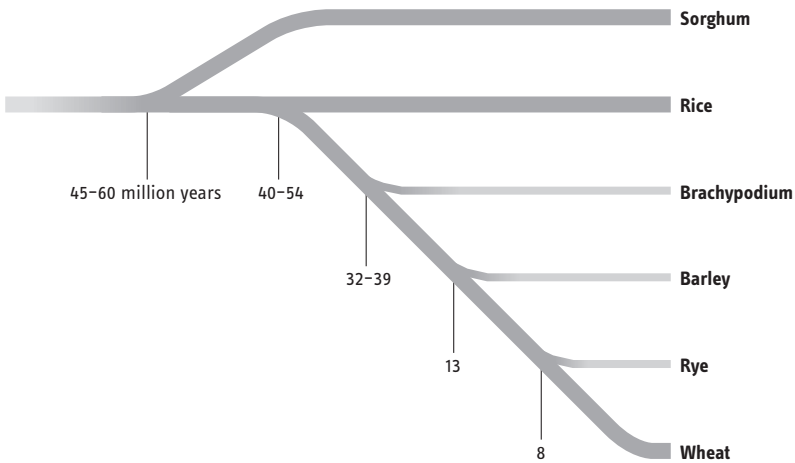
Cooperation Partners / Authors

Helmholtz Zentrum München Georg Haberer, Manuel Spannagl, Klaus Mayer, Heidrun Gundlach — **The International Brachypodium Initiative (principal investigators): USDA-ARS Western Regional Research Center, Albany** John P. Vogel — **USDA-ARS Plant Science Research Unit and University of Minnesota, St Paul** David F. Garvin — **Oregon State University, Corvallis** Todd C. Mockler — **HudsonAlpha Institute, Huntsville** Jeremy Schmutz — **US DOE Joint Genome Institute, Walnut Creek and University of California Berkeley** Dan Rokhsar — **John Innes Centre, Norwich** Michael W. Bevan

For the genome analysis, the scientists of the International Brachypodium Initiative, used whole-genome shotgun sequencing. In this method, the DNA is broken into many small fragments for sequencing. Computer programs then re-assemble these sequenced fragments into a continuous sequence.

Because its sequence is now known, the genomic data of Brachypodium can contribute significantly to the analysis of the structural and functional genomics of the significantly more complex grass genomes, which comprise the nutritional basis for humans and animals. Brachypodium distachyon is a wild pooid grass, which is closely related to barley, wheat and rye. The pooid grass has a genome spanning 272 Mb; the genomes of the cultivated forms of barley and wheat are 20 to 60 times as large. Due to the size and complexity of all other grass genomes it was not possible until now to analyze these and compare them. This has now changed through the sequencing of Brachypodium: Knowing the ancestral gene order conserved in evolution we can now refine our search in other genomes. Such reference genes provide a kind of inventory list and order system, in which most of the genes even in the large genomes for example of barley and wheat can be found. The molecular data can thus be interpreted much more easily.

Evolutionary Tree of Important Cultivated Cereals



The evolutionary tree of different grass species shows the close relationship between Brachypodium and unsequenced cultivated grasses. The divergence of rice and sorghum took place about 45 to 50 million years ago. The divergence of Brachypodium, barley and rye occurred in more recent times.

The scientists discovered several ten thousand conserved genomic associations between Brachypodium, rice, sorghum and wheat. This similarity underscores the value of Brachypodium as a model plant for the functional genomics of cultivated grasses. Comparative genome analysis provides information e.g. on the development of the genome size, on the distribution and duplication of genes or on the evolution of entire chromosomes. Thus, it aids in identifying genes and elucidating their function.

The analysis of the Brachypodium genome is an essential step towards elucidating the most important cereal genomes and thus also the basis for the sustainable preservation of the basis of human nutrition. The new findings are an indispensable prerequisite for selectively breeding crops that are better adapted to changing environmental conditions.

The now completely sequenced wild pooid grass Brachypodium distachyon is a model plant for food and forage grasses. The plant is annual, fast growing, undemanding, relatively small with a height of 20 centimeters and is self-fertilizing. Originally endemic to the eastern Mediterranean, it can now be found in temperate zones across the globe.

Original Publication
The International Brachypodium Initiative: Genome sequencing and analysis of the model grass Brachypodium distachyon. Nature 463 (2010) 763-768 | doi:10.1038/nature08747

Clostridia Degrade Tar Oil Contaminants in Groundwater

"With my research, I want to contribute to a better understanding of microbial processes in groundwater, which are crucial for preserving this resource so important for our society."

For phylogenetic classification, scientists at the Helmholtz Zentrum München have identified microorganisms that degrade toluene in situ at a contaminated field site. In this way, the microorganisms contribute to the natural cleanup of contaminated sediments and aquifers. The innovative research approach based on ^{13}C-labeling can be applied to any contaminant and opens new possibilities for risk assessment in the water cycle.

Dr. Tillmann Lüders

2009 Tenure track evaluation at the Center — **since 2004** Group leader of the research group Molecular Ecology at the Institute of Groundwater Ecology, Helmholtz Zentrum München — **2002–2004** PostDoc in the Department of Biogeochemistry, Max Planck Institute of Terrestrial Microbiology, Marburg — **1999–2001** PhD, Max Planck Institute of Terrestrial Microbiology and the University of Marburg

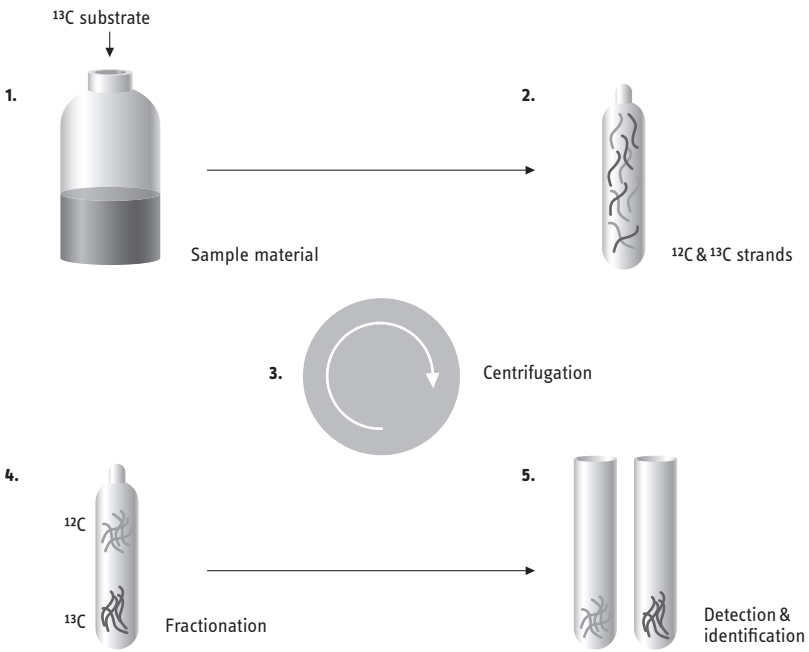
Cooperation Partners / Authors

Helmholtz Zentrum München Rainer U. Meckenstock, Frederick von Netzer, Holger Penning, Christian Winderl, Tillmann Lueders

Groundwater is the most important drinking water resource of our society and is thus of essential importance for human health. The world's groundwater resources are threatened by a variety of contaminations such as hydrocarbons, drugs or pesticide residues. Although specific microorganisms that can degrade such substances that are often toxic for humans are known from laboratory studies, it is largely unknown which particular organisms are involved in these processes in the environment, especially in anoxic groundwater.

Now for the first time, a research team led by Tillmann Lüders at the Helmholtz Zentrum München has identified a group of bacteria that degrade toluene in situ in a natural microbial community in the aquifer of a former coal gasification plant. An innovative labeling method with ^{13}C (SIP, stable isotope probing) for nucleic acids was used. Sediment samples with the natural microbial community were incubated in the laboratory under natural anaerobic conditions with ^{13}C-labeled toluene. Subsequently, total microbial DNA was isolated from this. By means of DNA gradient ultracentrifugation, the genomic DNA enriched with ^{13}C was resolved; it was then characterized by DNA fingerprinting and sequence analysis.

Stable Isotope Probing of Nucleic Acids (NA-SIP)



1. Sediment samples of natural microbial communities are mixed with ^{13}C-labeled toluene.
2. After prolonged incubation, total DNA is extracted from the sample. Only the bacteria that were involved in the degradation of toluene have incorporated the ^{13}C label into their DNA.
3. Density gradient centrifugation for separation of labeled and unlabeled DNA.
4. DNA enriched with ^{13}C, and therefore heavier (here: dark gray) is separated by fractionation from the unlabeled, lighter DNA (primarily ^{12}C, light gray).
5. In the ^{13}C-labeled DNA the toluene degraders are identified by PCR fingerprinting and sequencing.

Contrary to previous assumptions, the identified key organisms do not belong to the Deltaproteobacteria, already known as toluene degraders. Rather, they are related to Desulfosporosinus spp. within the Peptococcaceae, a subgroup of the Clostridia. So far, Clostridia have not yet been recognized as relevant sulfate-reducing degraders of contaminants in situ. They are usually viewed as fermenters, spore-formers and also as pathogens which cause e.g. gastrointestinal infections and botulism. As a consequence of this surprising classification of the microorganisms that are involved in contaminant degradation in situ, it will now be possible to elucidate the mechanisms underlying this important ecosystem service. Lüders' research results form the basis for approaches to stimulate microbial degradation of contaminants in groundwater and for innovative monitoring and management strategies at contaminated sites.

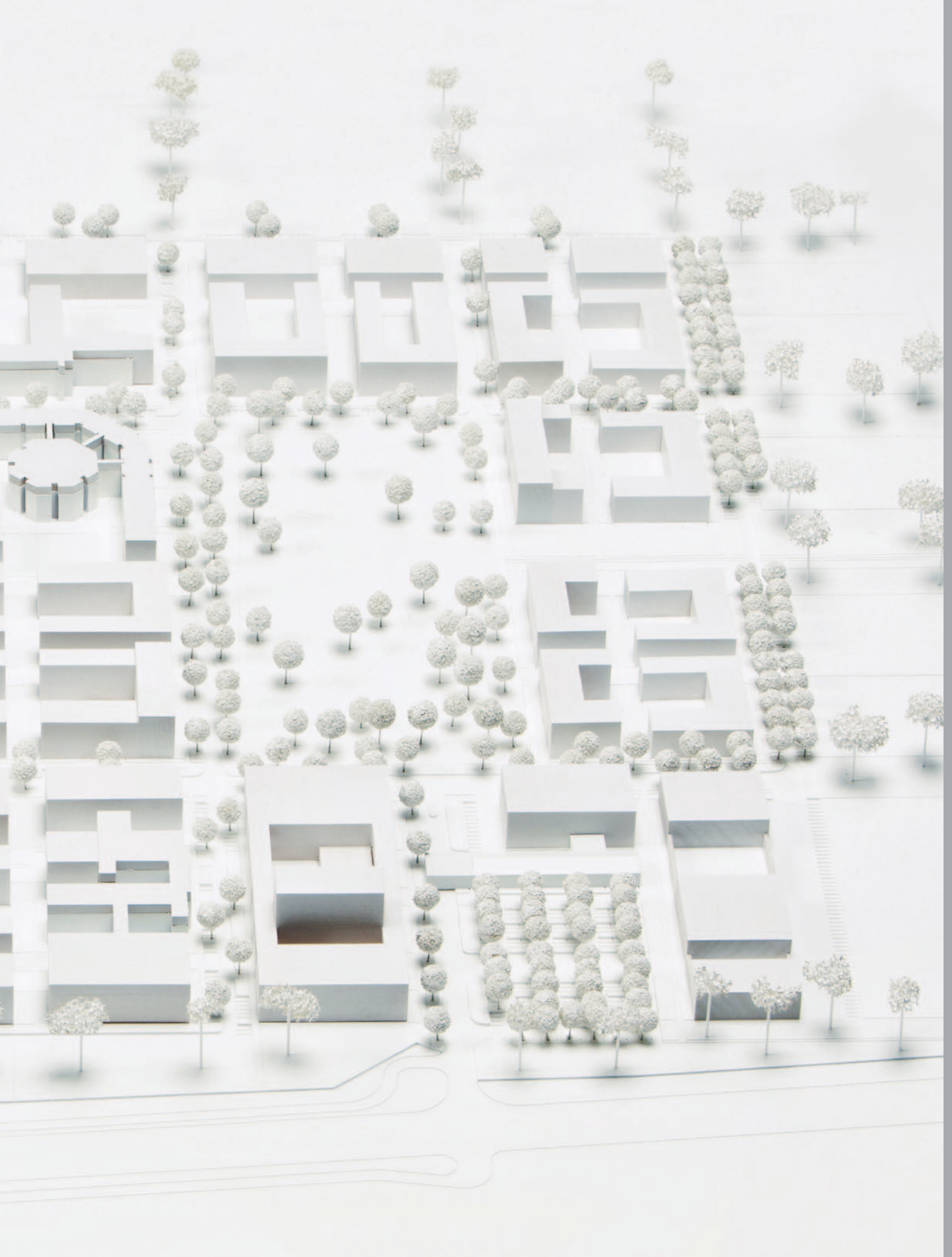
Toluene belongs to the substance category of aromatic hydrocarbons. Many substances of the category are considered carcinogenic and / or mutagenic. The ring-shaped molecules are chemically very stable and therefore can only be degraded by certain organisms. Toluene is found in petroleum and serves as a model compound for tar oil and other residues from coal gasification.

Original Publication
Christian Winderl et al.: DNA-SIP identifies sulfate-reducing Clostridia as important toluene degraders in tar-oil-contaminated aquifer sediment. The ISME Journal 4 (2010) 1314–1325 | doi:10.1038/ismej.2010.54

On the campus of the present-day Helmholtz Zentrum München, the experimental and training facility for radiation protection is established in 1960 as part of the Nuclear Research Center (GfK) in Karlsruhe. In 1964 it becomes an autonomous research center, the Gesellschaft für Strahlen- und Umweltforschung (GSF), under the jurisdiction of the Federal Ministry for Scientific Research. The Society's main task is to conduct preventive research for protection from nuclear radiation. From the mid-1960s, research is extended to include the biomedical field and the environmental field.

In 1971 the name is changed to Gesellschaft für Strahlen- und Umweltforschung. By expanding its foci to include environmental health care, epidemiological research and lung research, the largest German center for life sciences is created in Neuherberg. In 1990 the institution takes the next step in its development by changing its name to GSF – National Research Center for Environment and Health. In the following years the Center expands its activities in genome research and in the field of neurodegenerative diseases. In 2006 the Center begins its strategic re-orientation towards environmental health, which is consistently developed further in 2008 by changing its name to Helmholtz Zentrum München – German Research Center for Environmental Health.

The 52 hectare campus in the community of Oberschleißheim north of Munich has a multifaceted past. In the 19th century the Kingdom of Bavaria sets up a stockbreeding farm. At the beginning of the 20th century, the Marist Brothers run an educational establishment for young adults with social problems. The educational establishment is disbanded in 1934 and the grounds are used by the German Wehrmacht as a native veterinary park. After the war the ASID serum works use the federally-owned buildings for the production of vaccines. The lease agreement is terminated in 1959 and the grounds are made available for building the research center.



Campus Timeline

“The campus of Helmholtz Zentrum München is embedded in the moorlands to the north of Munich. It reflects the transformation processes that the Center has undergone in the five decades of its existence. By opting for landmark buildings in the moorlands, we want to express the identity of the present-day Center. An attractive campus attracts excellent scientists who conduct excellent research.”

The Campus before 1960

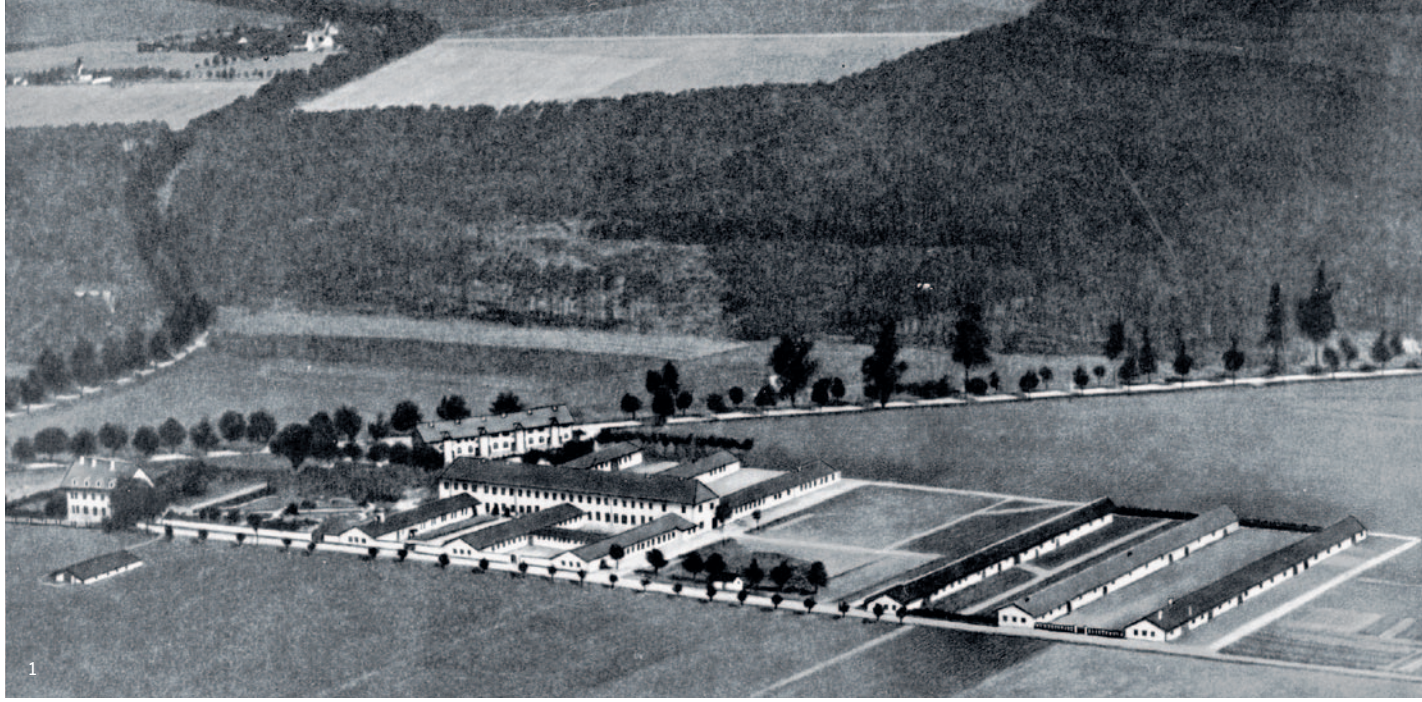
until 1934
Dormitory of the Sancta Maria educational establishment for boys: Until 1934 Marist Brothers run a home for young adults with social problems —1

The west wing of the dormitory houses the chapel of the educational establishment. —2

Stables and agricultural buildings: The home of the Marist Brothers includes horticultural and agricultural farms as well as a training workshop. —3

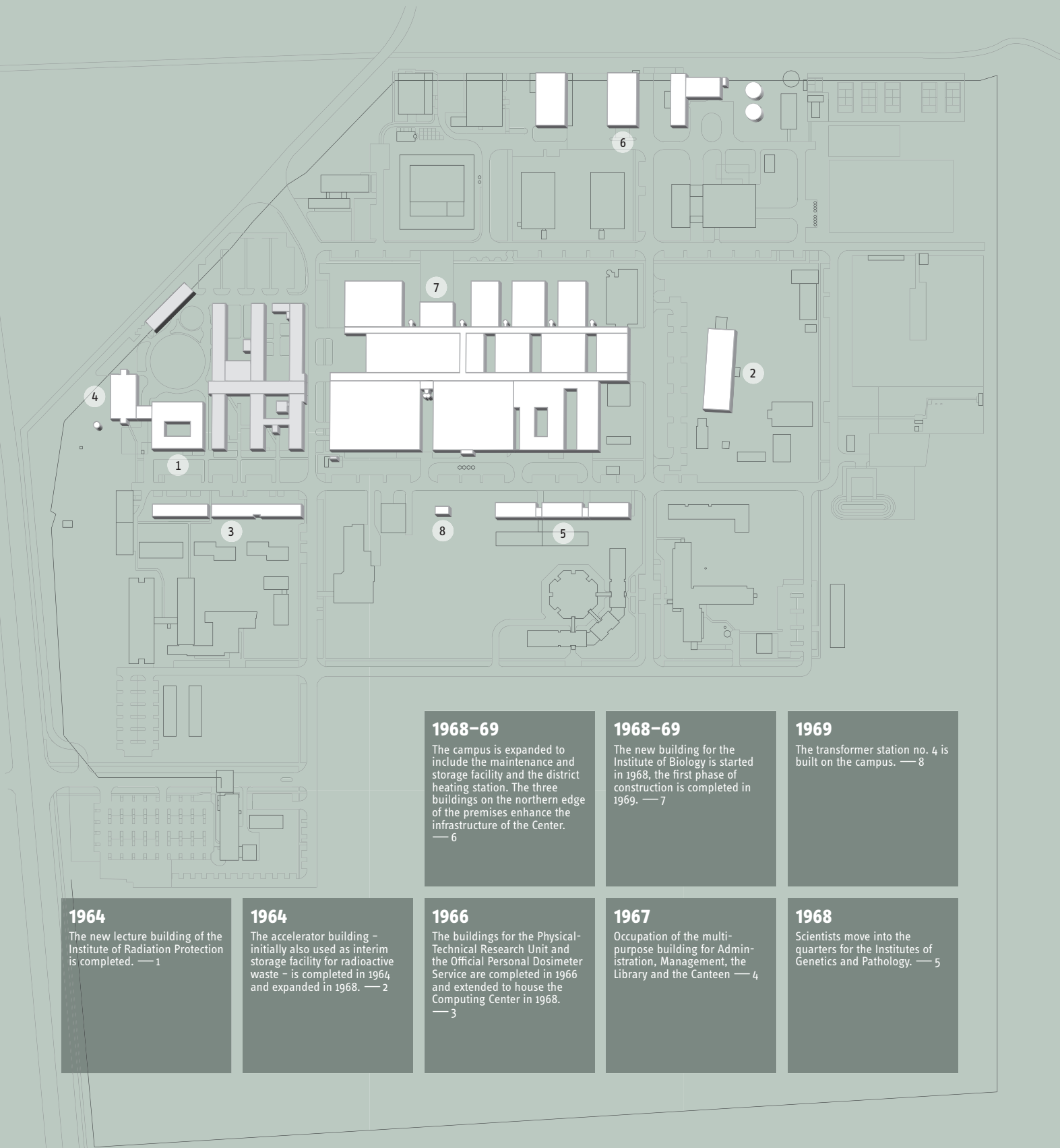
Staff apartments in the educational establishment, disbanded in 1934. —4

until 1960
Until the research center was established, the area served different purposes, e.g. as a veterinary park, refugee camp and serum factory.



1 Aerial view of Neuherberg before 1960 **2** Sancta Maria educational establishment for boys, run by the Marist Brothers, around 1925 **3** Reconstruction of the former stables **4** Map of present-day Neuherberg around 1860: Original position sheet for the topographic atlas of the Kingdom of Bavaria (position sheet no. 668 dated 1863, © Bayer. Vermessungsverwaltung; 2011) **5** Chapel of the Sancta Maria educational establishment, nowadays used as part of the institute

1960–1969



1964
The new lecture building of the Institute of Radiation Protection is completed. — 1

1964
The accelerator building – initially also used as interim storage facility for radioactive waste – is completed in 1964 and expanded in 1968. — 2

1966
The buildings for the Physical-Technical Research Unit and the Official Personal Dosimeter Service are completed in 1966 and extended to house the Computing Center in 1968. — 3

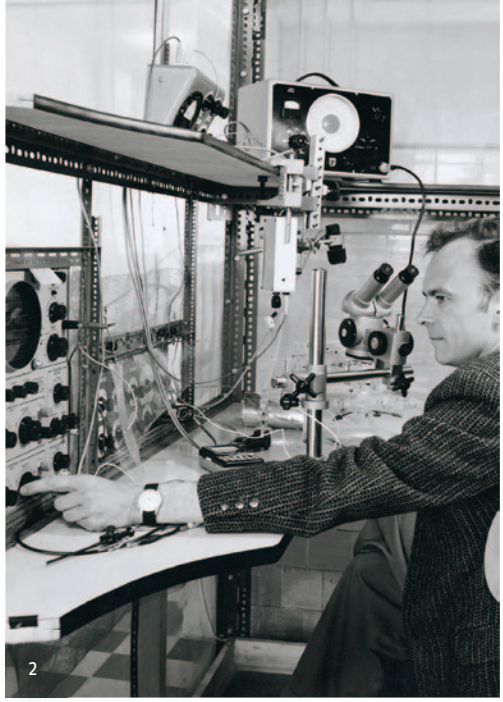
1967
Occupation of the multi-purpose building for Administration, Management, the Library and the Canteen — 4

1968
Scientists move into the quarters for the Institutes of Genetics and Pathology. — 5

1968–69
The campus is expanded to include the maintenance and storage facility and the district heating station. The three buildings on the northern edge of the premises enhance the infrastructure of the Center. — 6

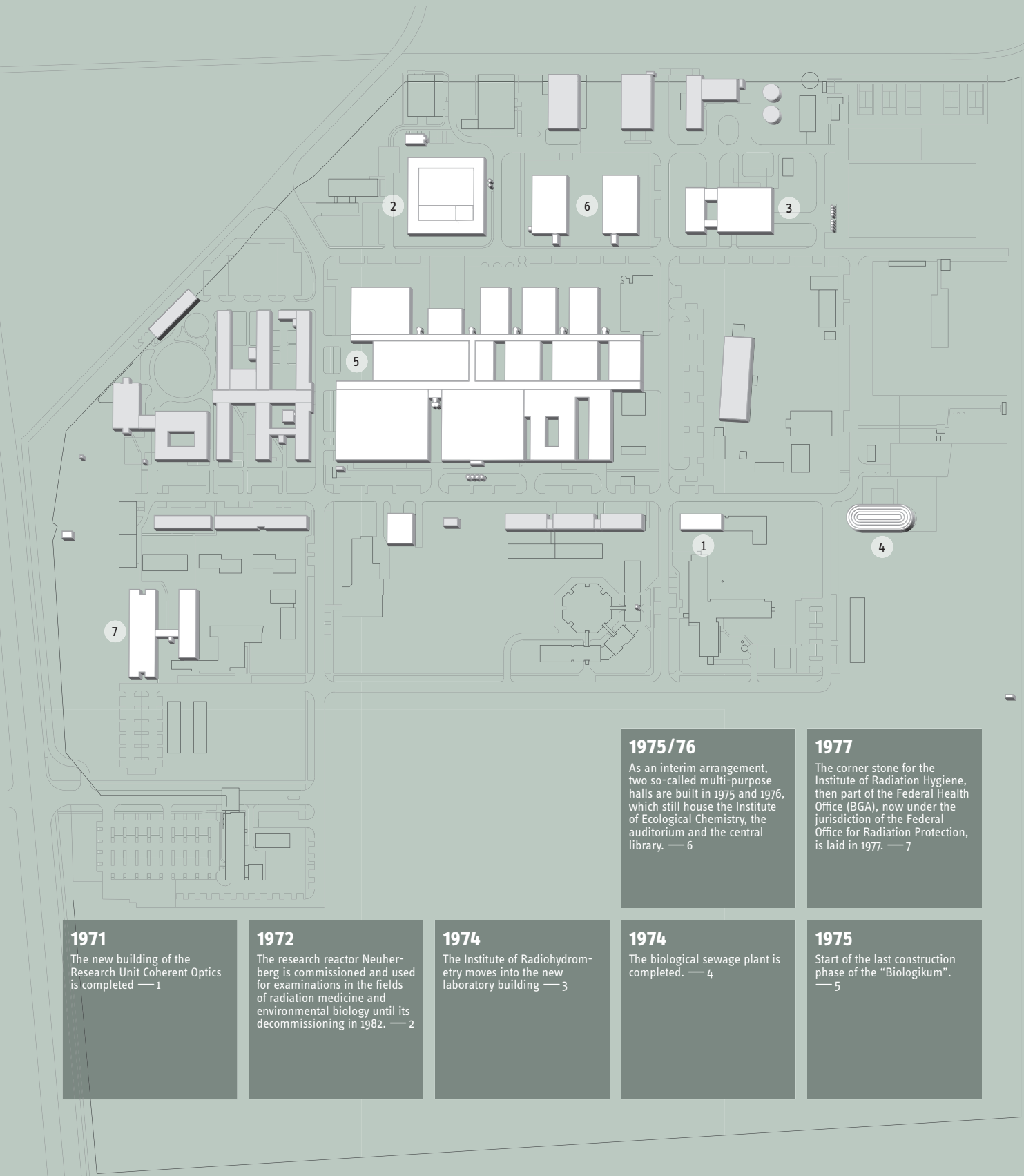
1968–69
The new building for the Institute of Biology is started in 1968, the first phase of construction is completed in 1969. — 7

1969
The transformer station no. 4 is built on the campus. — 8



1 Teaching requisite qualifications in radiation protection: A course participant in front of a radio paper chromatograph **2** Test set-up at the Institute of Radiation Protection **3** Electron microscope at the Institute of Hematology **4** At the Institute of Radiation Protection, course participants have been taught in practical matters of radiation protection since 1960 **5** Maintenance and storage facility and district heating station **6** Building site of the nuclear biology area, overlooking the administration building in the background **7** Facade of the lecture building for the Institute of Radiation Protection

1970–1979



1971
The new building of the Research Unit Coherent Optics is completed — 1

1972
The research reactor Neuherberg is commissioned and used for examinations in the fields of radiation medicine and environmental biology until its decommissioning in 1982. — 2

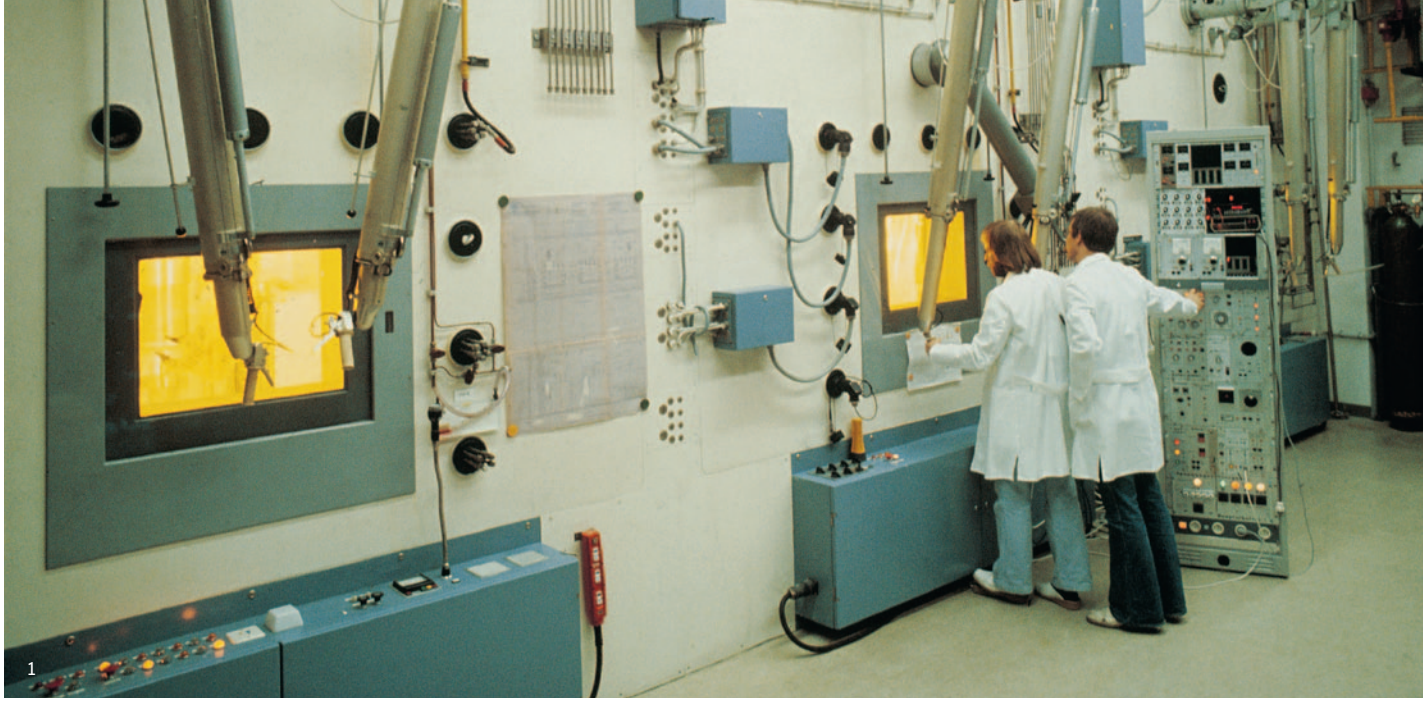
1974
The Institute of Radiohydrometry moves into the new laboratory building — 3

1974
The biological sewage plant is completed. — 4

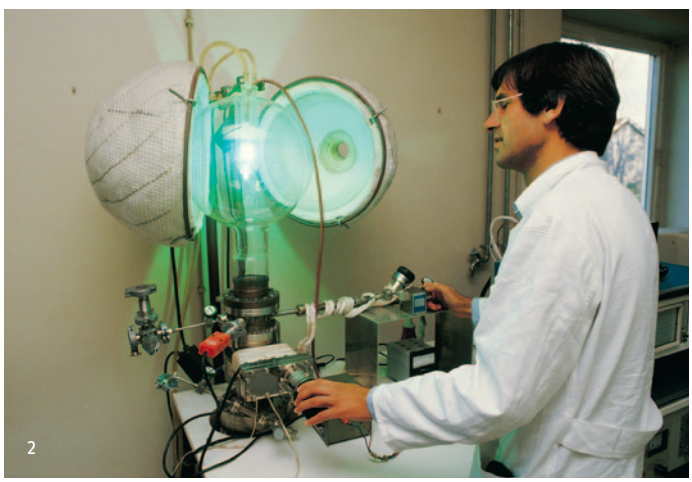
1975
Start of the last construction phase of the "Biologikum". — 5

1975/76
As an interim arrangement, two so-called multi-purpose halls are built in 1975 and 1976, which still house the Institute of Ecological Chemistry, the auditorium and the central library. — 6

1977
The corner stone for the Institute of Radiation Hygiene, then part of the Federal Health Office (BGA), now under the jurisdiction of the Federal Office for Radiation Protection, is laid in 1977. — 7



1 Neutron experiments at the research reactor Neuherberg **2** Photochemical breakdown of chemicals at bench scale **3** View from the new “Biologikum” to the West
4 Experiments on the fundamentals of medical laser application **5** Institute of Radiohydrometry



1980–1989

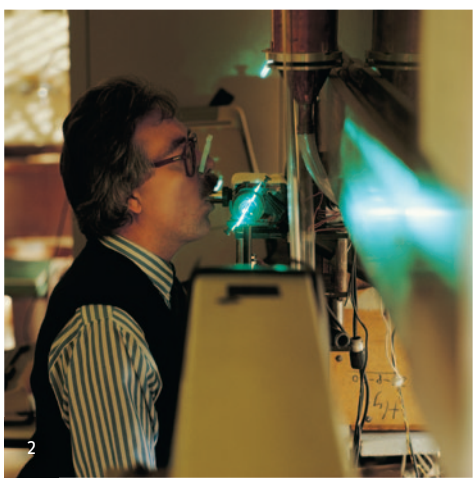
1981
The new building of the Institute of Medical Informatics and Systems Research is completed. The Computing Center is in the octagonal part. — 1

1981
The Technical Monitoring Center goes on line. — 2

1988
The entrance area is remodeled. — 3

1988
The Institute of Toxicology receives its own laboratory building. — 4

1 New building for the Computing Center and the Institute of Medical Informatics and Systems Research
2 Inhalation device for determining the particle deposits in the lung **3** Tests for the gas emission of timber preservatives into ambient air
4 Archiving of bio samples in the environmental specimen bank **5** Stele by Ben Muthofer in front of the Institute of Medical Informatics and Systems Research
6 Sculpture by Jochen Scheithauer at the main entrance road to the campus **7** Institute of Toxicology



1990–1999

1999
The Institute of Biomathematics and Biometry moves into its own building. — 6

1992
The canteen building at the entrance to the campus is completed and occupied

1994
The greenhouse of the Research Unit for Environmental Engineering is put into operation. — 2

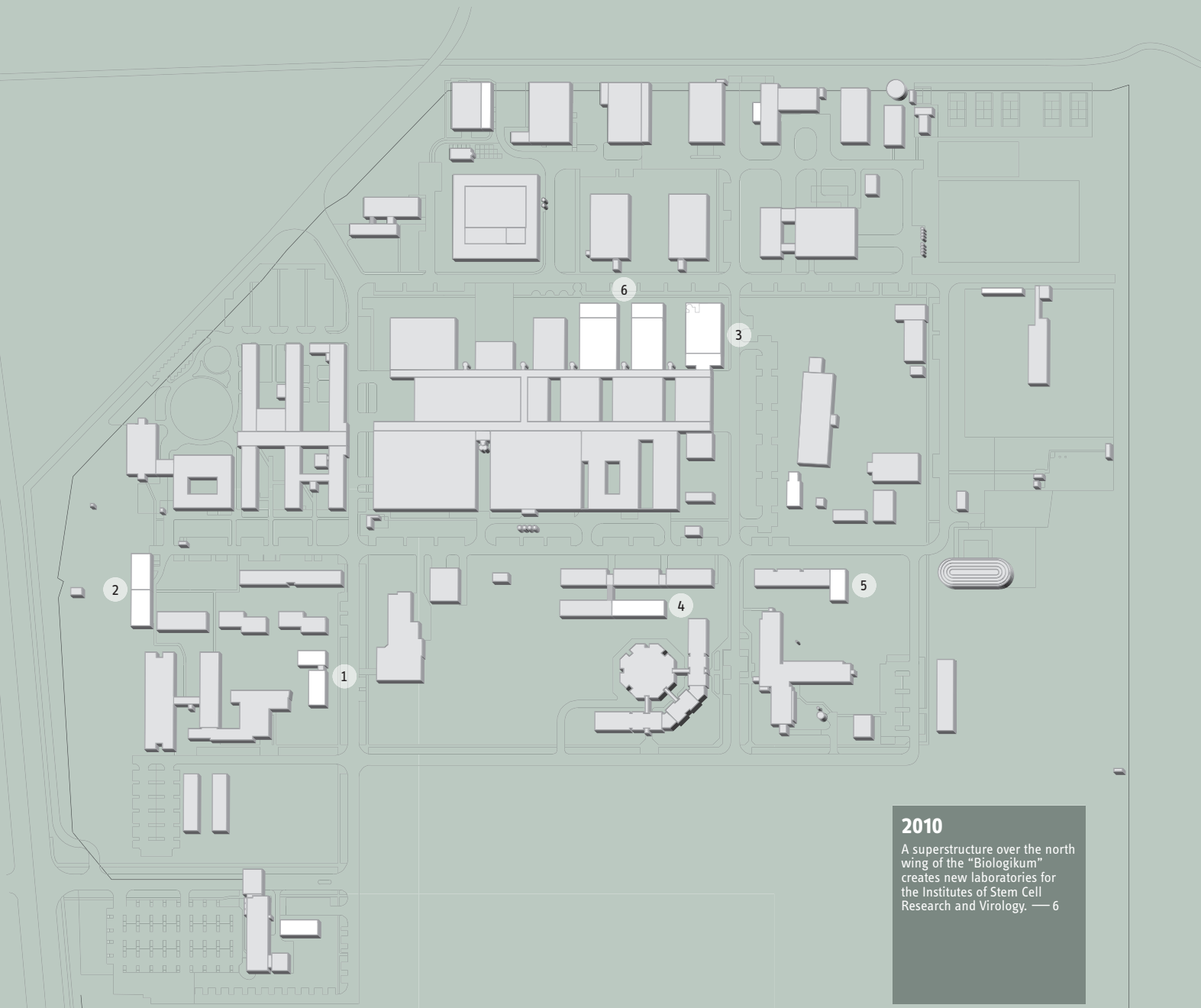
1996
The lysimeter plant commences operation. — 3

1999
The new building for the receiving office South is completed. — 4

1999
The Institute of Soil Ecology is extended. — 5

1 Air gas analysis for environmental simulation **2** Environmental remediation of chemically contaminated soils at bench scale
3 Research greenhouse for examining global environmental change **4** Sculpture “Limits of Development” in the entrance area of the campus
5 Test basement of the lysimeter plant **6** Canteen building **7** Virtual diagnosis of CT images at the Institute of Medical Informatics and Systems Research

2000–2010



2010
A superstructure over the north wing of the "Biologikum" creates new laboratories for the Institutes of Stem Cell Research and Virology. — 6

2001
The day care center is built in 2001 and expanded in 2005. — 1

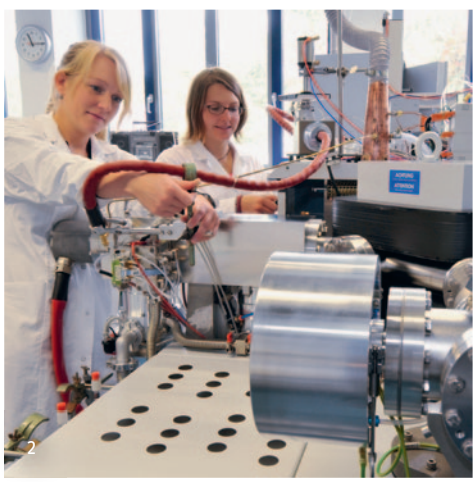
2003
The Official Personal Dosimeter Service moves into its own building, which now accommodates infrastructure facilities. — 2

2002
The "Biologikum" is extended by a laboratory building for the Institutes of Experimental Genetics, Developmental Genetics, and Human Genetics. — 3

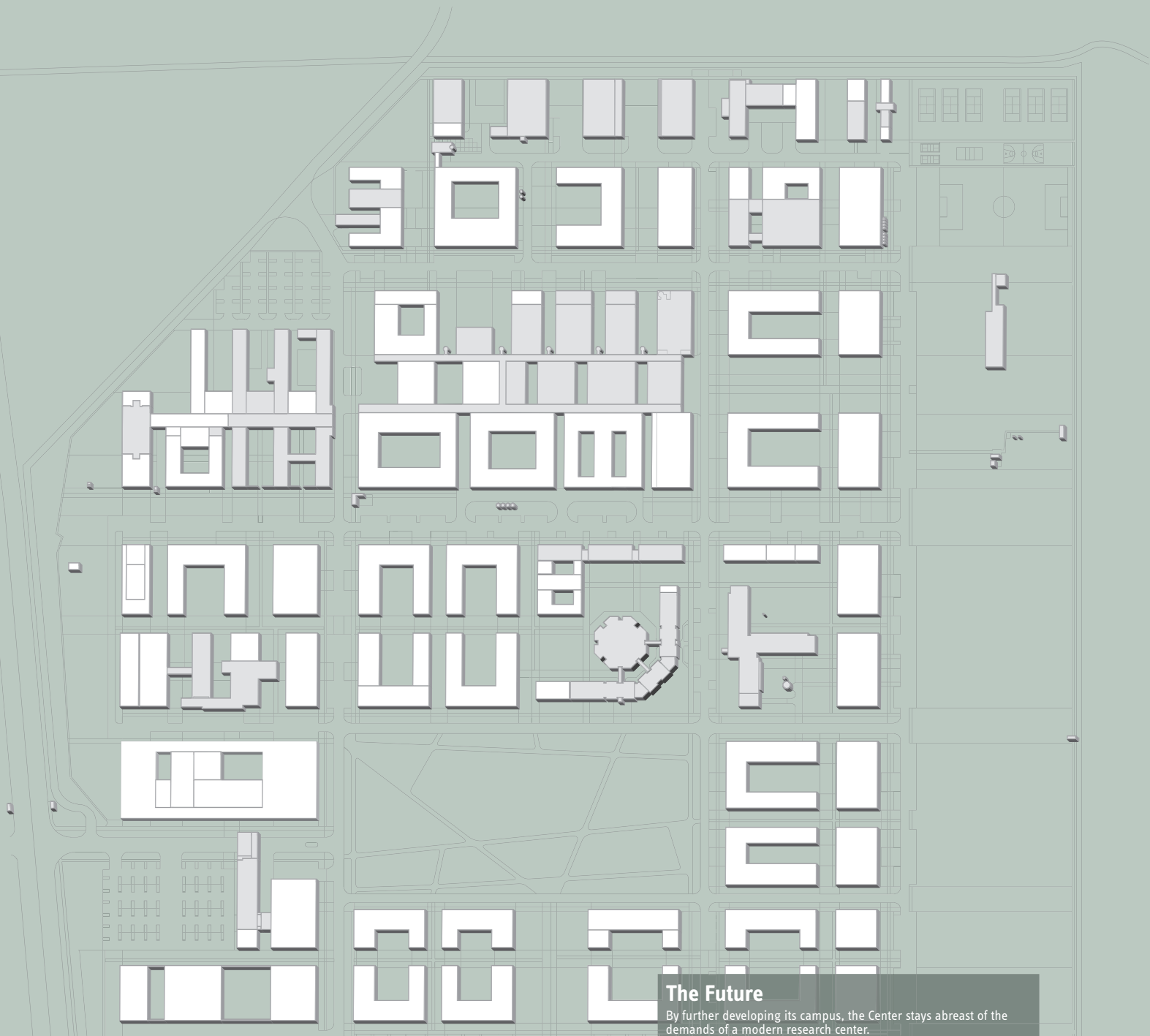
2009
The Institute of Structural Biology and the Institute of Biological and Medical Imaging move into their own buildings. — 4

2009
An extension is built for the NMR devices of the Institute of Structural Biology and Ecological Chemistry. — 5

1 EUCOMM laboratory at the Institute of Experimental Genetics 2 Measurement laboratory at the Institute of Groundwater Ecology 3 Core Facility Genome Analysis Center 4 Map section of Neuherberg nowadays (aerial view © Bayer. Vermessungsverwaltung 2011) 5 New building of the Institutes of Structural Biology as well as Biological and Medical Imaging 6 Extension for the Center's Institutes of Genetics



The Future of the Helmholtz Zentrum München Campus

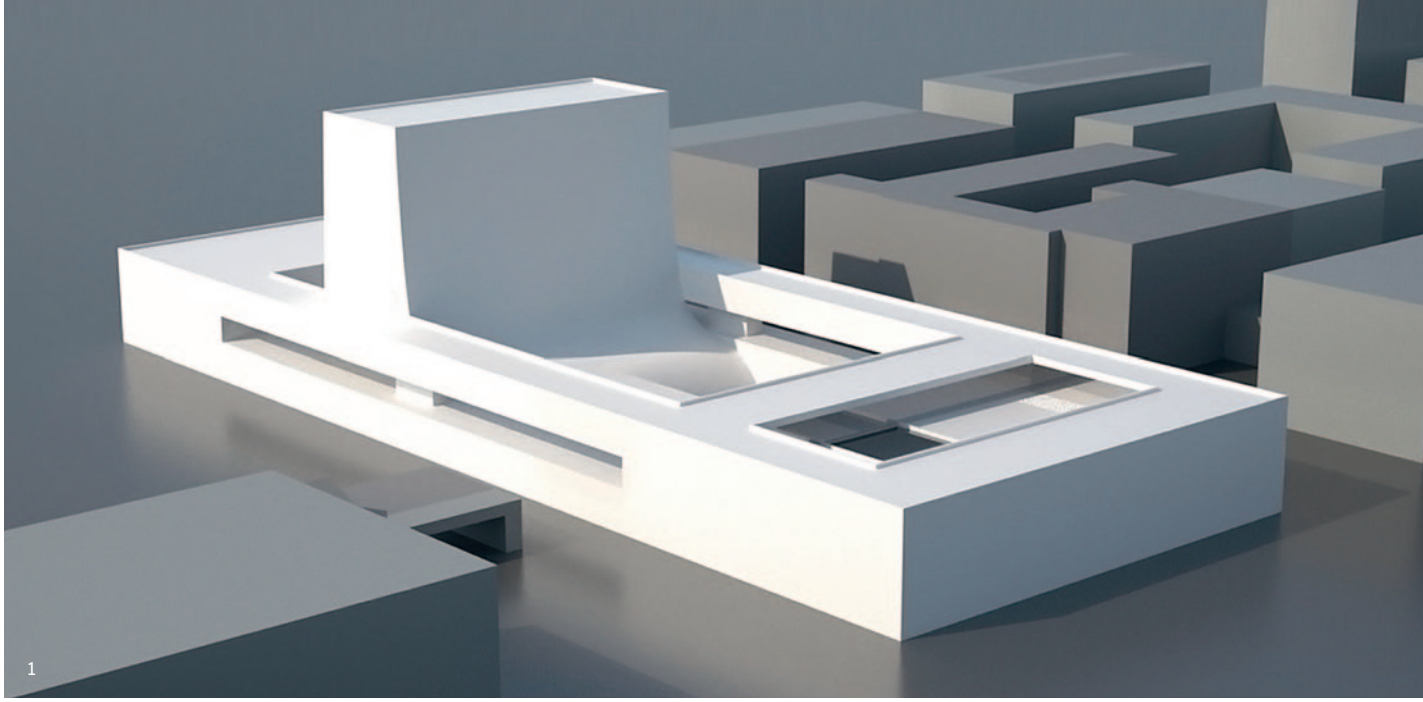


The Future

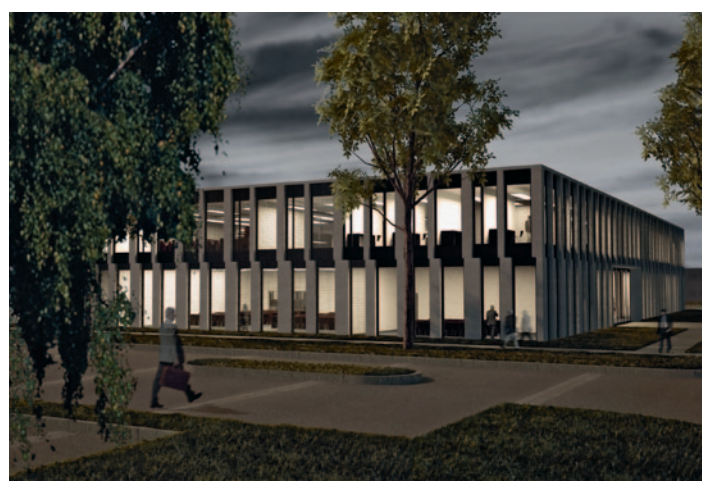
By further developing its campus, the Center stays abreast of the demands of a modern research center.

The renovation of existing buildings will take into account energy efficiency, and the development in the north-western area will be intensified. New buildings required for the strategic re-orientation will be built.

Model for campus development: BRUNE ARCHITEKTEN BDA
www.helmholtz-muenchen.de/publikationen/mitarbeitermagazin/fruehjahr-2010/



1 Vision of a transfer building in the entrance area.
2 A reception area with a central park will link the Center with the outside world and create an urban atmosphere for work at the campus.



Facts

Organization and Transformation

Scientific institutions need efficient management if they are to focus on their scientific work. The increasing complexity brought about by the multitude of networks, cooperation at all levels and increasing organizational and thematic complexity require new approaches.

For a research center to be nationally and internationally successful, its administration must develop continuously. Administrative staff consider it their responsibility to ensure optimum working conditions for the scientists. The multitude of networks and cooperation at all levels and the increasing organizational and thematic complexity require continuous changes in the administrative organization.

In the context of new scientific impulses, Helmholtz Zentrum München adjusted its operational structures and decisions making processes in order to ensure the continued smooth operation of its scientific work. To this end our governance structure was changed in 2009 to allow for a quick and appropriate response to changing requirements.

Familiarity with the Subject for Operative Decisions

For operative decisions in networked structures, the principle of greater familiarity with the subject has proven successful. Therefore Helmholtz Zentrum München is driving the decentralization of administration ahead: In 2010 our decentralized administration was opened, with an office in Großhadern. Since then an office on the first floor of the "Hämatologikum" in Großhadern – within walking distance of the Comprehensive Pneumology Center (CPC) – has been supporting the development of the CPC in an administrative capacity, while also driving ahead the management of scientific re-orientation or restructuring processes.

Change Management: Support through the Changes

The new organizational structure is part of the Change Management, through which our employees were included in the systematic change. Following the introduction of the corporate mission of Helmholtz Zentrum München in 2009, we have continued to implement it in 2010.

At the same time a cross-departmental personnel development concept promotes systematic training and further education, for example in the areas of communications and methodological competence, management, and leadership. The departments Human Resources and Communication closely cooperate in the reception of new employees and provide them with profound insights into processes at the Center.

Science Management and Transformation
New forms of communication, such as the staff magazine "imZentrum", introduced at the end of 2009, support the cultural change: In addition to up-to-the-minute reports, the staff magazine reveals scientific and administrative correlations and places research results in their strategic context.

Guidance in the Process of Transformation
In addition, regular meetings of senior and middle management were organized in 2010 in order to discuss current and strategic developments. One example are the goals of the Center, which were introduced in 2009 as part of management by objectives. They are connected with the annual staff appraisals and allow the Center to implement the performance-oriented pay set out in the Collective Agreement for the Public Service (TVÖD). Management by objectives supports the Center's transformation and creates a common level of understanding between management and staff regarding the next steps and the future direction. Thus all staff members learn to what extent each individual project contributes to the overall objectives.

This promotes transparency and identification, and thus also solidarity between administration and science. These steps provide guidance in the process of transformation and allow management to contribute to the endeavored goal of Helmholtz Zentrum München: one^{2013} – one Center, one goal.

Staff

In 2010 Helmholtz Zentrum München employed 1879 people from over 50 different nations. 33 percent of these employees were financed by third-party funding. Over three quarters of the staff work in the scientific arena – including 307 doctoral students, 131 postdocs and 476 scientists focusing on the fields of biology, (bio)chemistry, physics and medicine.

The key to a company's success are its employees. This is particularly true in research, where we are dependent on the work of excellent scientists in order to keep up with global competition. To this end it is necessary to create suitable structures to attract the brightest employees.

Equal Opportunities
One of the milestones on this path is equal opportunity. The Center has already received the Total E-Quality certificate for equal opportunities on two occasions and aims to increase its share of female employees. Women now make up more than 50 percent of the staff at Helmholtz Zentrum München. Since 2002 the proportion of female scientists at the Center has increased from 37 percent to 47 percent. In 2010 30 percent of our management positions were held by women.

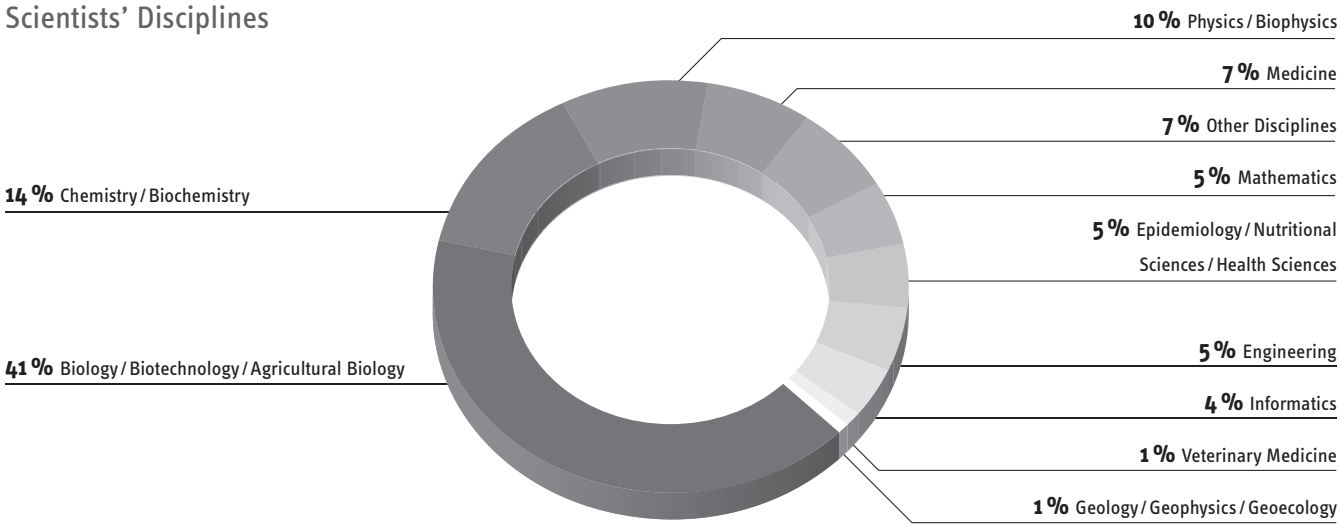
Staff Development
Independent and responsible employees are the key to successful scientific work. The Center has therefore developed a systematic HR development strategy. Junior researchers assume responsibility for staff and projects early on as well as receiving further training for management positions.

HELENA – Investment into the Future
In order to provide optimum support for doctoral students, Helmholtz Zentrum München, Ludwig-Maximilians-Universität (LMU) Munich and Technische Universität München (TUM) established the first Helmholtz Graduate School for Environmental Health (HELENA) in 2010. This offers doctoral students ideal training conditions and networks, with an internationally unique focus on environmental health.

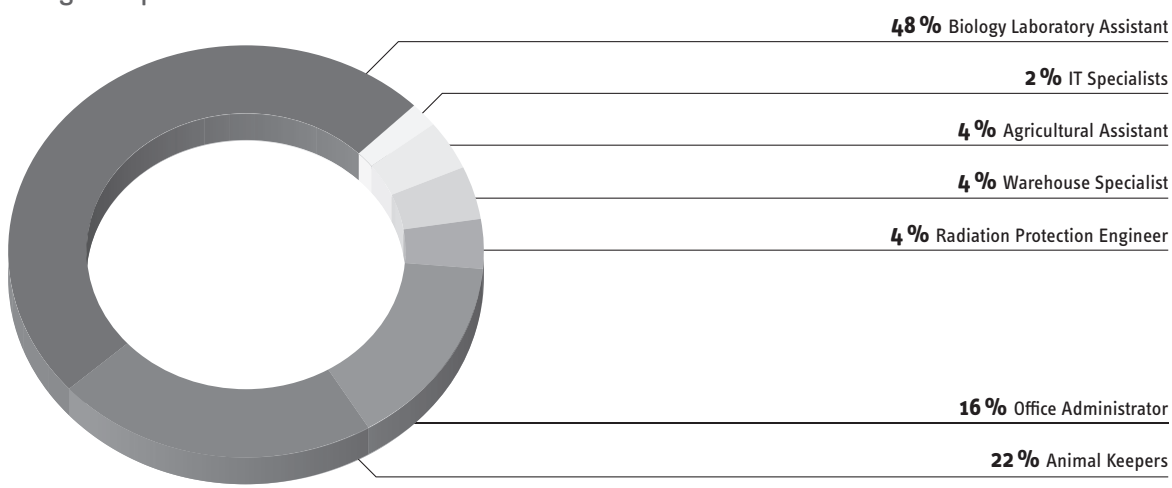
Vocational Training
In addition to supporting junior researchers, Helmholtz Zentrum München also offers a wide range of trainee positions: At the end of 2010, 46 trainees were employed in commercial and technical occupations and as future animal keepers.

Distribution of Staff by Area of Work

Scientists' Disciplines



Vocational Training Disciplines



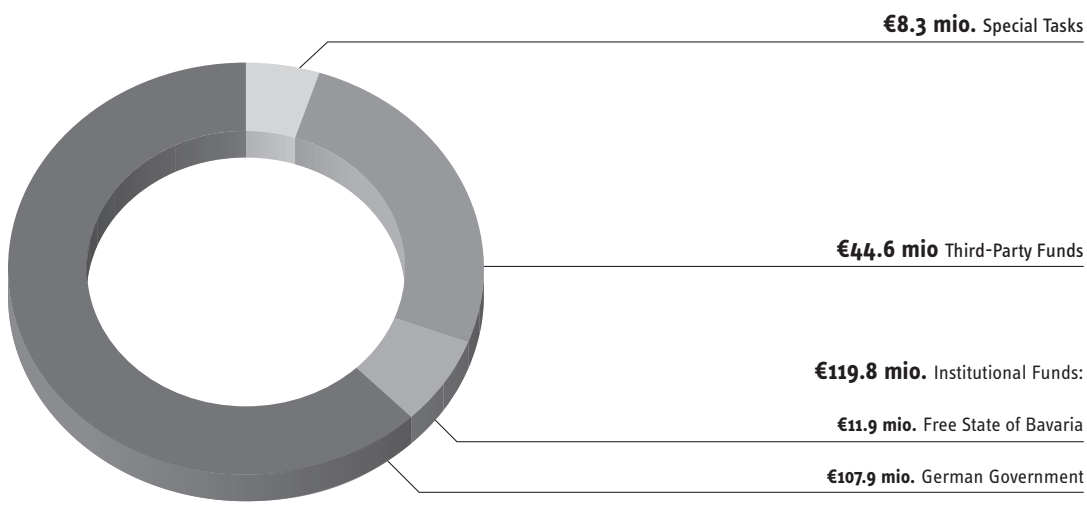
Finances

In 2010, the overall budget of Helmholtz Zentrum München amounted to 172.7 million euros, with 119.8 million euros coming from institutional funding provided by the German Government and the Free State of Bavaria at a ratio of 90:10. The remaining part of the budget consists of third-party funds of national and international origin, which were raised by the Center for specific projects.

Since 2003, the research centers of the Helmholtz Association have been financed by means of program-oriented funding (POF). These programs are applied for and funded for five years. After successful evaluation for the current second phase (2009-2013), Helmholtz Zentrum München is presently involved in two programs in the research area "Health" and one program in the research area "Terrestrial Environment".

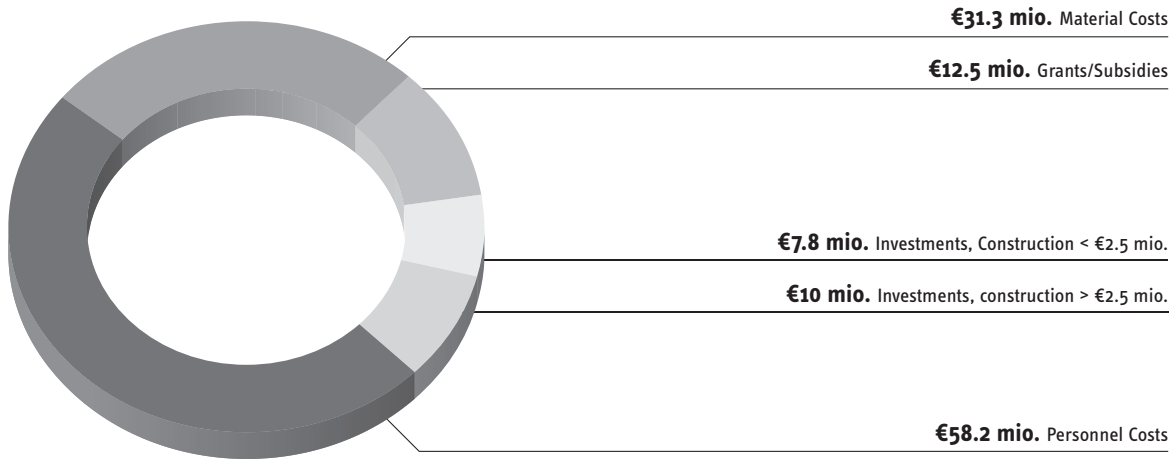
Total Funding by Source of Funds in 2010
Overall €172.7 mio.

Year-end figures as of May 13, 2011



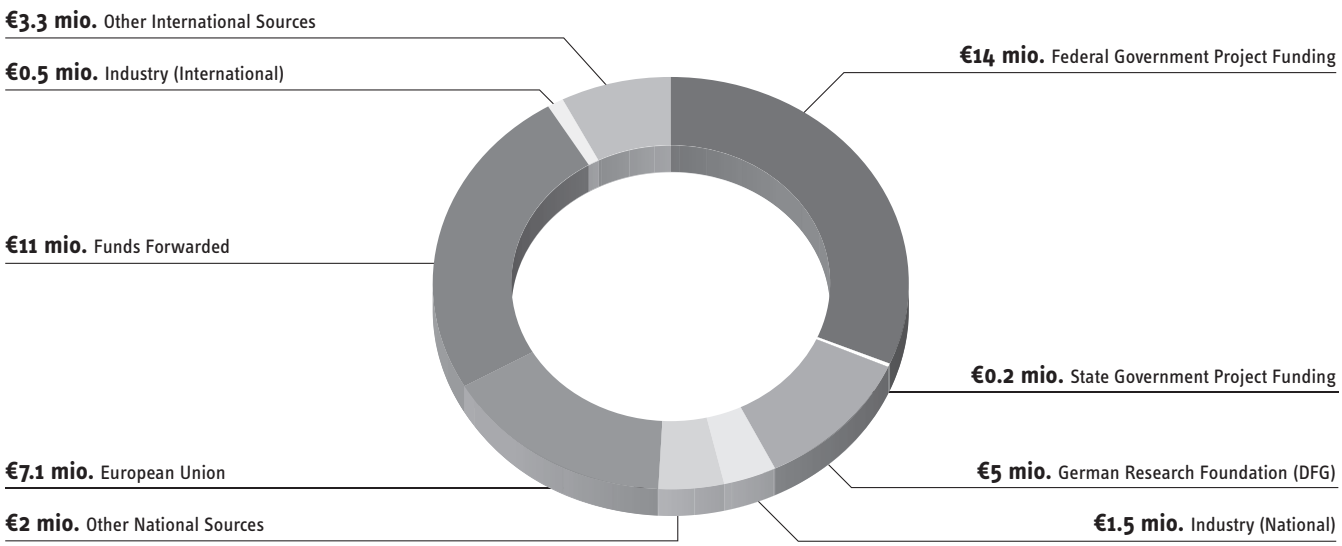
Institutional Funding in 2010
Overall €119.8 mio.

Year-end figures as of May 13, 2011



Third-party Funding According to Source – 2010
Total Amount for Research Tasks €44.6 mio.

Total reflected values as of: April 19, 2011



Plus special tasks totaling **€8.3 mio.**
(= operation of Official Personal Monitoring Service)

Project Funding

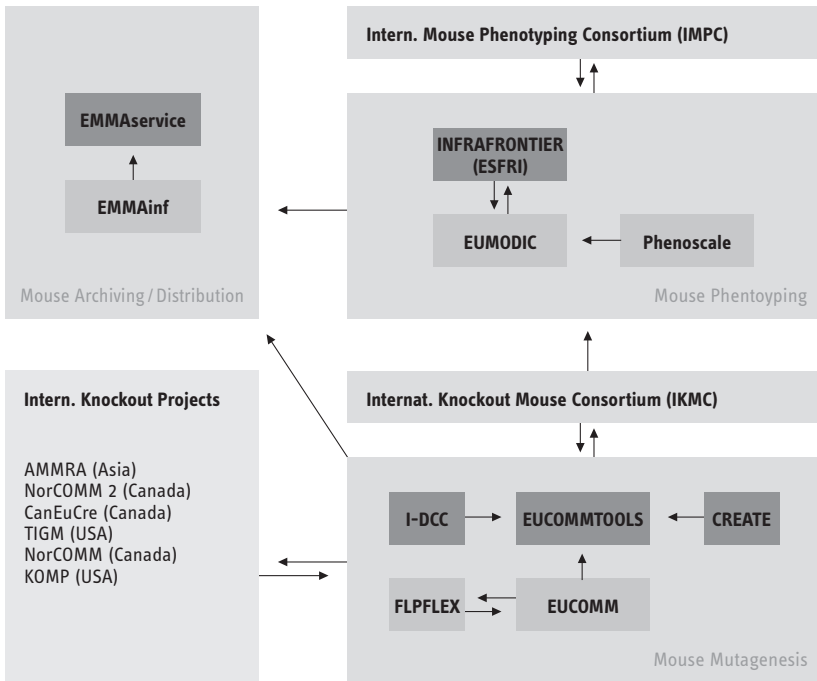
Helmholtz Zentrum München successfully participates in calls for proposals by the Federal Ministry of Education and Research, the European Research Framework Program, the German Research Foundation, the Helmholtz Association of German Research Centers and other public and private institutions. In 2010, a total of 44.6 million euros were raised for research. After deduction of 11.0 million euros, which were forwarded, 33.6 million euros remained for research at the institute. This is equivalent to a share of approximately 28 percent of institutional funding.

Funding by the German government ranked highest with 14.9 million euros, followed by 7.1 million euros from the European Union and 5.0 million euros from the German Research Foundation (DFG). Overall, Helmholtz Zentrum München had more than 400 contracts in 2010 for third-party funds for research projects. To date, 75 projects with EU funding amounting to over 38 million euros have been approved for Helmholtz Zentrum München as part of the 7th Framework Program of the European Union. The Center's participation in the ERC's EU Starting Grant excellence initiative in the area of basic research proved particularly successful. After Heiko Lickert from the Institute of Stem Cell Research received a grant for diabetes research in the second call, four scientists of the Center won a grant in the third call – Melanie Königshoff, Comprehensive Pneumology Center, for lung regeneration – Mathias Heikenwälder, Institute of Virology, for inflammation induced liver tissue destruction and carcinogenesis – Daniel Razansky, Institute of Biological and Medical Imaging, for deep tissue optoacoustic imaging – and Fabian Theis, Institute of Bioinformatics and Systems Biology, for improving models for systems biology. For the implementation of their groundbreaking ideas, funding amounting to a total of over 6.6 million euros is available.

For years now Helmholtz Zentrum München has been participating successfully in the successive Research Framework Programs of the European Union. It has thus increased its international visibility, expanded its scientific competences, strengthened its networks, and raised significant funds.

Particularly impressive examples of the Center's successful participation across several framework programs are the establishment and development of a global network for the generation and characterization of mouse models for human diseases, and projects for risk evaluation in the low dose range at EURATOM.

Mouse Models: EU Funding 2002 until Today

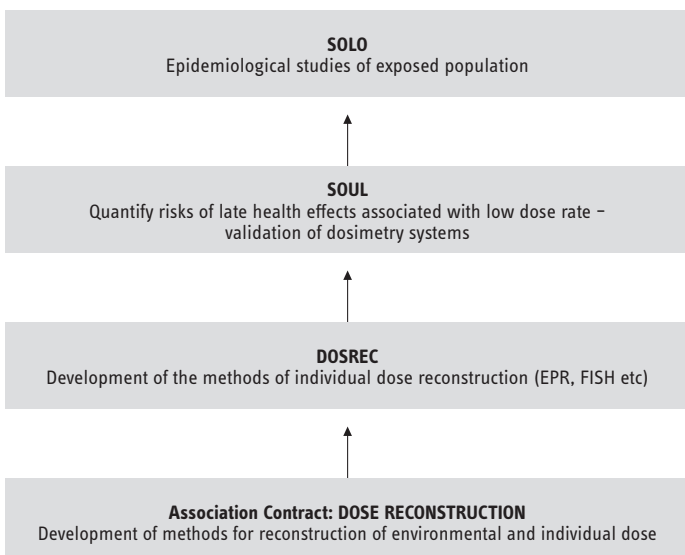


Participation of Helmholtz Zentrum München in EU projects from Framework Program (FP) 6 and 7 researching mouse mutagenesis, mouse phenotyping and archiving, with the objective of achieving a functional annotation of all genes for health and disease.

The total funds for the projects described amount to over 76 million euros. They began with the projects EUMORPHIA for functional genomics in mouse models, and EMMA for mouse archiving in FP5, which successfully continue in the current start-up funds for the preparatory phase of a pan-European research infrastructure in the area of phenotyping and archiving of models of mammalian genomes in FP7 (INFRAFRONTIER).

The projects EMMA, EUCOMM and INFRAFRONTIER, coordinated at Helmholtz Zentrum München, have contributed significantly to the establishment of a global mouse mutagenesis and phenotyping cluster. The network encompasses international knockout projects from the USA, Canada and Asia as well as international networks such as the International Knockout Mouse Consortium (IKMC) and the International Mouse Phenotyping Consortium (IMPC). The INFRAFRONTIER initiative from the ESFRI process (European Strategy Forum on Research Infrastructure) is currently promoted by the participating countries through considerable national funds.

Evaluation of the Radiation Risk: EURATOM Projects 1994 until Today



EURATOM projects for evaluating the radiation risk and developing tools to determine and reconstruct radiation in the low dose range.

Helmholtz Zentrum München is involved in various projects for the development and refinement of measurement methods in order to be able to extrapolate individual human and organ doses directly in a person, for a risk evaluation based on epidemiological studies. The development of these methods forms the basis of research into the radiation risk at low doses and for modeling carcinogenesis.

Using the projects for model development depicted here, EU projects with 157 partners have been conducted since FP5 in order to determine the health risk posed by low radiation doses. FP5: GENRISK, GENRAD, GENRAD-T, Low dose risk models, FP6: Risc-Rad, Note, Alpha-risk, Genrisk-T, FP7-DoReMi, Epi-RadBio, Cardiorisk, STORE. The SOUL project under FP6 was coordinated by the Center. To date the EU has provided overall funds amounting to approximately 60 million euros for method development and evaluation of the radiation risk in the low dose range.

Participation of Helmholtz Zentrum München in Projects Funded by DFG in 2010

Through the coordinated programs of the German Research Foundation (DFG), Helmholtz Zentrum München has established close regional networks in the health sector with both Munich universities and the Max Planck Institutes of Biochemistry and Neurobiology. With a total of 33 individual projects, the Center – together with Ludwig-Maximilians-Universität and Technische Universität München – is involved in nine collaborative research centers / transregios. Munich thus plays a leading role, along with Berlin, as a cluster location for research in Germany.

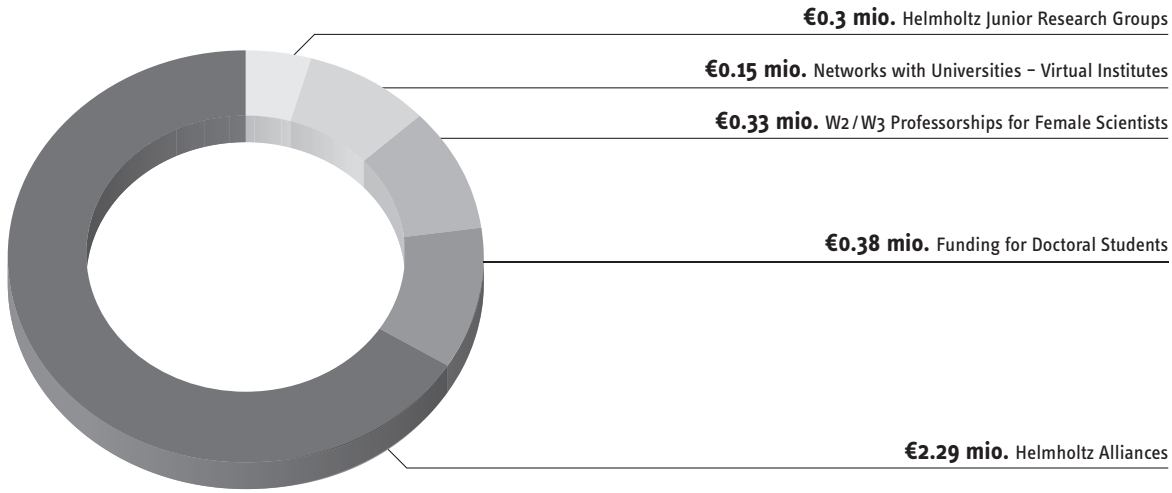
Funding Program	Projects
6 Collaborative Research Centers and 3 Transregios	33
6 Priority Programs	7
4 Research Groups	8
Leibniz Prize	1
Emmy-Noether	1
EURYI-Award	1
Individual Funding	34

Through its participation in programs of the Federal Ministry of Education and Research (BMBF), Helmholtz Zentrum München contributes significantly to current matters of great importance to society and the economy. Important joint research projects that were successfully attracted in 2010:

- For the establishment and implementation of the German institutions for INFRAFRONTIER (The European Infrastructure for Phenotyping and Archiving of Model Mammalian Genomes), coordinated by Martin Hrabě de Angelis, Institute of Experimental Genetics, the BMBF provided 17 million euros.
- The KORA-AGE 2 project, coordinated by the Institute of Epidemiology I, aims to identify factors contributing to health in old age, employing a longitudinal analysis. Approximately 3 million euros are available for this research.
- Radionuclides in the environment and their transport in the food chain to and in human beings are the focus of the projects coordinated by the Institute of Radiation Protection as part of the Competence Alliance Radiation Research II. The funding amounts to 1.7 million euros.
- The Institutes of Human Genetics and Experimental Genetics are actively involved in the OSTEOPATH project, which deals with new mouse models for investigating osteoporosis and molecular-genetic research of the phosphate metabolism. For this research the Center receives funding amounting to 0.7 million euros.

Funds Raised by the Center in 2010 from the Initiative and Networking Fund (IVF)

after deduction of all funds forwarded



In the course of establishing the German Centre for Diabetes Research in 2009 and developing diabetes research as an important core issue of Helmholtz Zentrum München, a further consolidation of third-party funds for diabetes research could be achieved. While third-party funds in 2008 still stood at approximately 1.5 million euros, they rose to approximately 3.7 million euros in 2009 and 2010 respectively.

International Cooperation

In 2010 Helmholtz Zentrum München was involved in around 1200 international cooperation projects with universities, non-university research institutions and industrial partners in 60 countries. These are the result of over 650 funding and cooperation agreements, bilateral programs for visiting scientists, and joint work and publications. The United States of America rank first in the list of international cooperation, followed by Canada, China and Japan. Cooperation within Europe focuses on Great Britain, France, Italy, Austria, Switzerland, Spain, Belgium, and the Netherlands.

In 2010 the Center received around 5.9 million euros from the Initiative and Networking Fund (IVF) of the Helmholtz Association of German Research Centers. After deduction of all funds forwarded to project partners, 3.5 million euros remained at the Center. The majority of these funds went to the three Helmholtz Alliances "Mental Health in an Ageing Society", "Systems Biology", and "Immunotherapy". The share of funds from the IVF for sponsoring doctoral students was greatly increased. A total of 3.0 million euros for six years were raised for the Helmholtz Graduate School for Environmental Health (HELENA). HELENA opened its doors on November 1, 2010 and will offer its doctoral students a structured Ph.D. course in eight pre-determined thematic fields, working in cooperation with Technische Universität München and Ludwig-Maximilians-Universität. The Helmholtz Research School "Lung Biology and Diseases" also received 1.5 million euros from IVF for a period of six years. Other new developments in 2010 were the Helmholtz junior research group "Inflammation induced chronic tissue destruction" under the leadership of Mathias Heikenwälder, the funding for Annette Ziegler, Institute of Diabetes Research, as part of the program for excellent female scientists, and the spin-off InfoDabble, set up by the Institute of Bioinformatics and Systems Biology.

Management

of Helmholtz Zentrum München since 1960

1960–1964
Prof. Dr. Otto Hug
Scientific Director

1960–1981
Prof. Dr. Rudolf Wittenzellner
Scientific Director, from 1964
Scientific-Technical Director

1964–1967
Dr. Rudolf Kriele
Administrative Director

1967–1968
Dr. Günter Lehr
Administrative Director

1968–1972
Dr. Walter Schulte-Meermann
Administrative Director

since 2005
Prof. Dr. Günther Wess
CEO and President

since 2006
Dr. Nikolaus Blum
CFO

1995–2005
Prof. Dr. Dr. Ernst-Günter Afting
Scientific-Technical Director

1999–2006
Dr. Hans Jahreiß
Administrative Director

1990–1995
Prof. Dr. Joachim Klein
Scientific-Technical Director

1988–1998
Dr. Carl-Heinz Duisberg
Administrative Director

1981–1990
Prof. Dr. Hans Wolfgang Levi
Scientific-Technical Director

1983–1988
Dr. Wolfgang Grillo
Administrative Director

1972–1978
Hermann Costa
Administrative Director

1978–1983
Dr. Rainer Gerold
Administrative Director

Overview of the Research Units and Institutes and joint appointments with Ludwig-Maximilians-Universität (LMU) Munich and Technische Universität München (TUM)

As of: April 2011

Environmental Health Program

Institute of Epidemiology (EPI I)
Director: **Prof. Dr. Dr. H.-Erich Wichmann** wichmann@helmholtz-muenchen.de
Chair of Epidemiology at Ludwig-Maximilians-Universität Munich

Institute of Epidemiology (EPI II)
Director: **Prof. Dr. Annette Peters** peters@helmholtz-muenchen.de

Institute of Genetic Epidemiology (IGE)
Director: **Prof. Dr. Konstantin Strauch** strauch@helmholtz-muenchen.de
Chair of Genetic Epidemiology at Ludwig-Maximilians-Universität Munich

Research Unit Molecular Epidemiology (AME)
Head: **Prof. Dr. Thomas Illig** illig@helmholtz-muenchen.de

Research Unit Gene Vectors (AGV)
Head: **Prof. Dr. Wolfgang Hammerschmidt** hammerschmidt@helmholtz-muenchen.de

Institute of Health Economics and Health Care Management (IGM)
Director: **Prof. Dr. Reiner Leidl** reiner.leidl@helmholtz-muenchen.de
Chair of Health Economics and Health Care Management at Ludwig-Maximilians-Universität Munich

Institute of Clinical Molecular Biology and Tumor Genetics (KMOLBI)
Director (acting): **Prof. Dr. Wolfgang Hammerschmidt**
hammerschmidt@helmholtz-muenchen.de

Institute of Clinical Molecular Biology and Tumor Genetics
Research Unit Molecular Epigenetics
Head: **Prof. Dr. Dirk Eick** eick@helmholtz-muenchen.de

Institute of Lung Biology (iLBD /CPC)
Director: **Prof. Dr. Oliver Eickelberg** oliver.eickelberg@helmholtz-muenchen.de
Chair of Experimental Pneumology at Ludwig-Maximilians-Universität Munich

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Director: **Prof. Dr. Dolores Schendel** schendel@helmholtz-muenchen.de

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Chair of General Pathology and Pathological Anatomy at Technische Universität München

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Chair of Radiation Biology at Technische Universität München

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Research Unit Radiation Cytogenetics (ZYTO)
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Research Unit Medical Radiation Physics and Diagnostics (AMSD)
Head: **Prof. Dr. Christoph Hoeschen** christoph.hoeschen@helmholtz-muenchen.de

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Chair of Toxicology and Environmental Hygiene at Technische Universität München

Institute of Toxicology
Research Unit Cellular Signal Integration (AZS)
Head: **Dr. Daniel Krappmann** daniel.krappmann@helmholtz-muenchen.de

Institute of Virology (VIRO)
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Systemic Analysis of Multifactorial Diseases Program

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Chair of Biomathematics at Technische Universität München

Institute of Biomathematics and Biometry
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Head: **Dr. Wolfgang Graf zu Castell-Rüdenhausen** castell@helmholtz-muenchen.de

Institute of Developmental Genetics (IDG)
Director: **Prof. Dr. Wolfgang Wurst** wurst@helmholtz-muenchen.de
Chair of Developmental Genetics at Technische Universität München

Research Unit Zebrafish Neurogenetics (ZEN)
Head (acting): **Prof. Dr. Wolfgang Wurst** wurst@helmholtz-muenchen.de

Institute of Experimental Genetics (IEG)
Director: **Prof. Dr. Martin Hrabě de Angelis** hrabe@helmholtz-muenchen.de
Chair of Experimental Genetics at Technische Universität München

Institute of Experimental Genetics
Research Unit Genome Analysis Centre (GAC)
Head: **Prof. Dr. Jerzy Adamski** adamski@helmholtz-muenchen.de

Institute of Human Genetics (IHG)
Director: **Prof. Dr. Thomas Meitinger** meitinger@helmholtz-muenchen.de
Chair of Human Genetics at Technische Universität München

Research Unit Protein Science (PROT)
Head: **Prof. Dr. Marius Ueffing** marius.ueffing@helmholtz-muenchen.de

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Director: **Prof. Dr. Magdalena Götz** magdalena.goetz@helmholtz-muenchen.de
Chair of Physiological Genomics at Ludwig-Maximilians-Universität Munich

Institute of Structural Biology (STB)
Director: **Prof. Dr. Michael Sattler** sattler@helmholtz-muenchen.de
Chair of Biomolecular NMR Spectroscopy at Technische Universität München

Research Unit Comparative Medicine (AVM)
Head: **PD Dr. Markus Brielmeier** brielmeier@helmholtz-muenchen.de

Institute of Diabetes Research Type 1 (IDF1)
Director: **Prof. Dr. Anette-Gabriele Ziegler** anette-g.ziegler@helmholtz-muenchen.de

Terrestrial Environment Program

Institute of Biochemical Plant Pathology (BIOP)
Director: **Prof. Dr. Jörg Durner** durner@helmholtz-muenchen.de
Chair of Biochemical Plant Pathology at Technische Universität München

Institute of Biochemical Plant Pathology
Research Unit Environmental Engineering (EUS)
Head: **Prof. Dr. Jörg-Peter Schnitzler** jp.schnitzler@helmholtz-muenchen.de

Institute of Soil Ecology (IBOE)
Director: **Prof. Dr. Jean Charles Munch** munch@helmholtz-muenchen.de
Chair of Soil Ecology at Technische Universität München

Institute of Soil Ecology
Research Unit Terrestrial Ecogenetics (TEG)
Head: **Prof. Dr. Michael Schloter** schloter@helmholtz-muenchen.de

Institute of Groundwater Ecology (IGOE)
Director: **Prof. Dr. Rainer Meckenstock**
rainer.meckenstock@helmholtz-muenchen.de
Chair of Groundwater Ecology at Technische Universität München

Research Unit Microbe-Plant Interactions (AMP)
Director: **Prof. Dr. Anton Hartmann**
anton.hartmann@helmholtz-muenchen.de

Institute of Ecological Chemistry (IOEC)
Director (acting): **Prof. Dr. Ralf Zimmermann**
ralf.zimmermann@helmholtz-muenchen.de

Institute of Ecological Chemistry
Research Unit BioGeoChemistry and Analytics (BGCA)
Head: **PD Dr. Philippe Schmitt-Kopplin**
schmitt-kopplin@helmholtz-muenchen.de

Institute of Ecological Chemistry
Cooperation Group "Comprehensive Molecular Analytics" (CMA)
Head: **Prof. Dr. Ralf Zimmermann**
ralf.zimmermann@helmholtz-muenchen.de

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www.helmholtz-muenchen.de

Editorial Office
Communications Department
Cordula Klemm, Dr. Brigitte Keller, Sven Winkler
presse@helmholtz-muenchen.de

Authors
Dr. Claudia Borchardt-Tuch, Dr. Hans H.Guldner,
Dr. Monika Offenberger,
a-quadrat corporate communications

Translation
Cornelia Benson, www.bts-berlin.com
Carol Oberschmidt, www.c-l-s.net

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Photographs
Martin Nink, www.ninkphoto.de
Ulla Baumgart, Michael Haggenmüller,
Michael van den Heuvel, Ingo Kniest, Jan Roeder

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Helmholtz Zentrum München
German Research Center
for Environmental Health

Ingolstädter Landstrasse 1
85764 Neuherberg, Germany
Phone: +49 (0)89 3187-0
Fax: +49 (0)89 3187-3324
www.helmholtz-muenchen.de

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ASSOCIATION