At a glance.
Helmholtz Zentrum München is currently organized in 39 research institutes and independent units, which are linked via programs and topics. The Center has various technology platforms and central service units. In order to facilitate the transfer of results from basic research into medical applications, scientists of Helmholtz Zentrum München collaborate closely in translational centers and clinical cooperation groups with medical partners at Munich’s universities and hospitals.

- 22 joint appointments with the Munich elite universities
- 18 spin-offs since 1997
- 39 institutes and independent research units
- 315 patent families
- 150 doctoral students
- 2234 employees
- 111 clinical cooperation groups
- 328 trans-lational centers
- 111 junior research groups
- 111 trainee places in 8 professions
- 1062 publications in international journals 2012
- 1178 publications in international journals 2013
- 224 million euros finance volume 2013
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Promotion of Young Scientists at Helmholtz Zentrum München – a Success Model

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Promotion of Young Scientists at Helmholtz Zentrum München – a Success Model

Helmholtz Zentrum München has consolidated its position as one of the world’s leading institutions in the field of health and the environment. In summer 2013 this was the assessment of the expert review for the third period of program-oriented funding, which provides the framework for our scientific work. In its review report, the panel of international experts commended the Center for its outstanding research achievements and strategic positioning. In addition, the reviewers specially commended the Center’s efforts to promote young scientists. In particular, they pointed to the Helmholtz Graduate School Environmental Health (HELENA), established only three years ago together with Technische Universität München and Ludwig-Maximilians-Universität, as an international success model. Currently, approximately 330 young people are working under the umbrella of HELENA in interdisciplinary teams toward their PhD degrees and are acquiring additional skills for future leadership positions in science and industry.

As a major theme in this biennial report, we present examples of our successful training program for young scientists. Read on page 32 how doctoral students use the opportunities of the Helmholtz Graduate School Environmental Health to begin their academic or professional careers.

Another focus of the promotion of young scientists at Helmholtz Zentrum München is on the appointment of talented young researchers to head their own junior research groups. Equipped with their own budgets and with responsibility for their own staff, the researchers can establish themselves internationally in their subject area within a period of five years. In 2012 and 2013, 13 junior research groups were launched. Altogether, there are 19 junior research groups at the Center, 13 of which are headed by women. Seven of these are funded by Starting Grants of the European Research Council. Starting on page 38 we present six junior research groups. At the same time, each portrait stands for a topic of the research programs of the Center.

At the end of 2013, the Center closed a gap in its strategic concept to promote young scientists with the first call for applications for an international postdoctoral program. Up to 16 excellent young scientists will develop and implement their personal career plan over the course of three years, within the framework of this program and with the support of scientific mentors and personal coaches.

An important component of talent management at Helmholtz Zentrum München is the promotion of well-trained science administrators, who serve as bridge between the needs of the research and the requirements of the administration. Oriented on the strategic objectives of its research, the Center offers its young professionals in science, administration and infrastructure a wide range of qualification opportunities. On page 112 you can read how Helmholtz Zentrum München promotes talented young people in science administration.

Of course, the focus of our work is on successful research and the publication of research results in international journals. Both the number of publications and their impact ranking have risen steadily in recent years. In 2012, 1062 publications with 6298 impact points resulted from research at the Center. In 2013 the publication output increased to 1178 publications and 7568 impact points. Since 2005 the Center has nearly doubled the number of its publications and has tripled its impact factors. As highlights of the Center’s scientific work, we present 34 selected publications starting on page 54.

Research at Helmholtz Zentrum München has successfully met the criteria of scientific evaluation. In doing so, the Center has never lost sight of its overarching objective: to contribute to a better understanding of gene-environment associated diseases and to the development of new therapies – especially for widespread common diseases such as diabetes, lung diseases and allergies. To ensure that progress in knowledge rapidly benefits society, translational research and innovation are key elements of our strategy. Two examples of particularly promising approaches in cancer treatment and for the prevention of type 1 diabetes can be found on page 104.

In 2013 Helmholtz Zentrum München achieved outstanding results in the review of its content and strategic development as well as its repositioning within the framework of program-oriented funding. Our task in the coming years will be to retain this position and to expand it further. Managing Directors Prof. Dr. Günther Wess, Dr. Nikolaus Blum and Dr. Alfons Enhsen explain in interviews starting on page 16 how we shall approach and master this task and describe the challenges that may lie ahead.

The Board of Directors would like to take the opportunity here to express its thanks to all employees of the Center and to the members of the Supervisory Board and the Scientific Advisory Board. All have contributed to the successful positioning of the Center internationally and to strengthening the Center for the future.

The Editors
Timeline 2012

**JANUARY 1st**

The Center expands allergy research. Under the direction of Prof. Dr. Carsten Schmidt-Weber – who at the same time holds the Chair of Molecular Allergology and Environmental Research at Technische Universität München – the newly founded Institute of Allergy Research is launched.

**JANUARY 3rd**

Focus on aerosols and health: To investigate the effects of anthropogenic particulate matter, Helmholtz Zentrum München, the University of Rostock and six other international partners join together to form the Helmholtz Virtual Institute of Complex Molecular Systems in Environmental Health (HICE).

**JANUARY 21st**

Outstanding achievement for epigenetic particulate matter: Helmholtz Zentrum München, the University of Rostock and six other international partners join together to form the Helmholtz Virtual Institute of Complex Molecular Systems in Environmental Health (HICE).

**FEBRUARY 1st**

Personalized therapies for diabetes: Helmholtz Zentrum München participates in the DIRECT project, which is funded by the Innovative Medicines Initiative (IMI) with 154 million euros.

**FEBRUARY 4th**

More intensive collaboration with INSERM: Researchers from Helmholtz Zentrum München and the French Institut National de la Santé et de la Recherche Médicale (INSERM) coordinate projects within the graduate program "Lung Biology and Disease".

**FEBRUARY 13th**

The Central Energy Facility celebrates its topping out ceremony: With the expansion of its utility infrastructure, the Center creates important conditions for the development of its Neuherberg research campus.

**MARCH 27th**

Presentation in Berlin of collaborative lung research success: The Parliamentary State Secretary in the Federal Ministry of Education and Research Dr. Helge Braun and the spokesperson of the German Center for Lung Research, Prof. Dr. Werner Seeger, present novel approaches to treat lung diseases. Photo: Ingo Kienst

**APRIL 12th**

The Helmholtz Research School of Lung Biology and Disease opens.

**APRIL 19th**

Alexander von Humboldt Professorship awarded to Matthias Tschope: Federal Research Minister Dr. Annette Schavan presents the most highly endowed international award for research in Germany to the director of the Institute for Diabetes and Obesity and chair of Metabolic Diseases at Technische Universität München.

**APRIL 28th**

Exploring the workplace: On nationwide "Girls’ Day", 10 school students gain insight into scientific work at Helmholtz Zentrum München.

**MAY 2nd**

Experts answer questions: The second patient forum of the Lung Information Service informs about childhood bronchial asthma at the Comprehensive Pneumology Center.

**MAY 3rd**

The Helmholtz Research School of Radiation Sciences is established: The new graduate school in a joint endeavor with the two Munich universities offers places for 25 PhD students and is part of the Helmholtz Graduate School Environmental Health (HELENA).

**MAY 11th**

Intensive cooperation: Under the leadership of its president Prof. Chunli Bai, a delegation of the Chinese Academy of Sciences informs itself about possibilities for expanding partnerships with Helmholtz Zentrum München.

**MAY 19th**

Diabetes institutes in Garching opened: Until the completion of the diabetes building in Neuherberg, the Institute for Diabetes and Obesity and the Institute of Diabetes and Regeneration Research are located on the Garching Business Campus.

**JUNE 15th**

Outstanding ranking: The epidemiologist Dr. Joachim Heinrich is ranked 12th in the world among most cited authors of asthma publications in the field of lung and respiratory research and 2nd among the German-language authors after the former director of the Institute of Epidemiology, Prof. Dr. Dr. H.-Erich Wichmann.

**JUNE 25th**

Good Clinical Practice: The Center awards its first Pionierpreis for Lung Research, Prof. Dr. Werner Seeger and the Fraunhofer Institute for Biomedical Engineering present the prize to 25-year-old student of clinical laboratory medicine Franziska Kölbl and Evelyn Thiel as well as warehouse logistics specialist Michaela Laumeyer who have completed their apprenticeships with top grades.

**JULY 11th**

Setting the course for the future: The Scientific Advisory Board endorses the Center’s strategies and concepts of its environmental health portfolio, public health and personalized medicine as well as their inclusion into the program-oriented funding of the Helmholtz Association (POF III).

**JULY 13th**

Green light for the specimen bank: The Supervisory Board approves the establishment and operation of the biobository for the National Cohort on the Neuherberg research campus.

**JULY 15th**

Investigation of the mechanisms of T cell tolerance: The Research Unit Molecular Immune Regulation, headed by Dr. Vigo Heissmeyer, begins operations.

**FEBRUARY 26th**

Good Clinical Practice: The Center establishes an internal policy for the production of clinical trial samples and for studies that are carried out together with clinical partners.

**FEBRUARY 28th**

Value creation strengthened: In addition to early-stage projects with value creation potential, the Department of Innovation Management, headed by Dr. Annette Janz, is now also responsible for the patenting and commercialization of innovative know-how.

**MARCH 27th**

First official visit to the Zugspitze: The Bavarian State Minister for Health and the Environment Dr. Marcel Huber informs himself in the environmental research station Schneefernerhaus about the contributions of Helmholtz Zentrum München to the European Virtual Alpine Observatory.
**Timeline 2012**

**JULY 18th**
The Department of Environmental Sciences begins work: The merger of seven research units contributes to the synergistic effects of environmental and health research at the Center.

**JULY 19th**
B2RUN corporate running competition in Munich: 168 runners from Helmholtz Zentrum München take part in the sports event in the Olympia Park.

**JULY 23rd**
Diabetes Information Service online: Under www.diabetesinformationsdienst-muenchen.de the Center makes information about diabetes available to the general public.

**JULY 24th**
Top marks for the administration: A nine-member panel of external experts presents its results of the review of planning, managing and support processes to the staff of the Center.

**AUGUST 1st**
Start of research campus: 50 children of staff take part in two-week holiday research program for kids on campus.

**AUGUST 14th**
Now a total of eight ERC Starting Grants at the Center: The European Research Council (ERC) awards a 1.5 million euro grant to Prof. Dr. Gil Gregor Westmeyer of the Institute of Biological and Medical Imaging and the Institute of Developmental Genetics to develop new methods of imaging molecular processes in the brain.

**AUGUST 28th**
Beyond Big Data: With Clueda AG, a new spin-off company from Helmholtz Zentrum München is launched. It develops software tools to strongly increase applicable knowledge and to read complex situations quickly.

**SEPTEMBER 14th**
MELODI Award for Dr. Kristian Unger: The scientist of the Research Unit of Radiation Cytogenetics receives in Helsinki the Multidisciplinary European Low Dose Initiative Prize, which is endowed with 4000 euros.

**SEPTEMBER 20th**
Development of young scientists is strengthened: The Helmholtz Association announces funding of two new junior research groups led by Dr. Stefanie Eyerich and Dr. Claudia Plant.

**OCTOBER 4th**
New trends in pulmonary medicine: The second Munich Lung Conference begins under the auspices of the Comprehensive Pneumology Center (CPC).

**OCTOBER 22nd**
The challenge of obesity: Within the framework of the World Health Summit in Berlin, CEO and Scientific Director Prof. Dr. Günther Wess moderates the discussion of renowned scientists.

**NOVEMBER 5th**
Epigenetic research receives VdFF Research Award: The Association of Friends and Sponsors (VdFF) awards a prize for interdisciplinary cooperation to a paper which appeared in Science in 2012 on the function of cell memory.

**NOVEMBER 6th**
Graduate Students’ Day: Prof. Dr. Erwin Neher, Nobel Laureate in 1991, holds a Career Lecture.

**NOVEMBER 12th**
Balancing career and family: The first parent-child room for short-term care needs is opened on campus.

**NOVEMBER 13th**
Campus Park takes form: With terrain modeling, work begins on the two-hectare meeting and recreation space.

**NOVEMBER 14th**
Launch of international competition for Health and Environment Funding: The Center funds internal projects on environmental health problems in the fields of allergies, the microbiome and health as well as nanoparticles with up to 180 000 euros per year.

**NOVEMBER 23rd**
Strategic alliance against obesity and diabetes: Helmholtz Zentrum München and Sanofi Aventis arrange a research alliance for new targets and screening methods to develop innovative therapy approaches.

**NOVEMBER 26th**
HICE Biomobile starts on first measuring campaign: At four European stations, scientists of Helmholtz Zentrum München, the University of Rostock and their partner institutions study the effects of particulate matter on lung cells.

**DECEMBER 10th**
Rapid publication of research results: Helmholtz Zentrum München and the German Center for Diabetes Research at Campus Neuherberg are partners in the publication of the newly established open access journal Molecular Metabolism.
Timeline 2013

JANUARY 1st
Coordinating role for the research field of Health: the CEO and scientific director of the Center, Prof. Dr. Günther Weiss, takes office as scientific vice-president of the Helmholtz Association and coordinator for the research field of Health.

JANUARY 3rd
Helmholtz researchers appointed to Radiation Protection Commission: Prof. Dr. Werner Rühm, head of the research group Personal Dosimetry of the Institute of Radiation Protection, belongs to the committee Radiation Risk and Dr. Werner Kichinger, company and fire department physician and head of the Regional Radiation Protection Center, belongs to the committee Emergency Response.

JANUARY 8th
Cooperation partners of the Center honored with Helmholtz International Fellow Awards: The Helmholtz Association conferred the awards, which are endowed with 20,000 euros each, to Prof. Dr. Harald von Boehmer, Harvard Medical School in Boston, and Prof. Dr. Nathan Kaminski, University of Pittsburgh.

JANUARY 15th
The Center expands its diabetes research capacity. The official opening of the Institute of Diabetes and Regeneration Research, directed by Prof. Dr. Heiko lickert, takes place in Garching. Lickert also holds the Chair of Diabetes Research/ Beta Cell Biology of Technische Universität München.

JANUARY 23rd
Funding notifications received: Helmholtz Zentrum München, Leibniz Institute of Plant Genetics and Crop Plant Research (IPK) Gatersleben and Forschungszentrum Jülich participate in the German Plant Phenotyping Network (OPPN) of the Federal Ministry of Education and Research.

JANUARY 30th
Vocational training completed: Michael Opitz, Willi Grätz, Markus Fischer and Alexander Felber successfully complete their final examination to become biology laboratory technicians.

FEBRUARY 14th
Joining forces for personalized medicine: As first German research institutions, Helmholtz Zentrum München joins the Personalized Medicine Coalition (PMIC), an international consortium of research, industry and patient organizations.

FEBRUARY 20th
With top marks in FOT III: International reviewers convince themselves of the quality and strategic relevance of the new research program Genes and Environment in Common Diseases within the framework of the program-oriented funding of the Helmholtz Association.

FEBRUARY 26th
Personalized assessment of the long-term effects of medical radiation exposure: Dr. Peter Jacob coordinates the research program “PASSOS”, which is financed by the Federal Ministry of Education and Research with around three million euros.

MARCH 1st
Gain for lung research: Prof. Dr. Jürgen Behr assumes the Chair of Pulmonary Medicine at Ludwig Maximilians-Universität München and becomes Director of Clinical Pulmonology at the Comprehensive Pneumology Center of Helmholtz Zentrum München, the LMU University Hospital and Askesips Specialist Clinics in Munich-Gauting.

MARCH 14th
Federal Minister Prof. Dr. Johanna Wanka confers Leibniz Prizes: Prof. Dr. Vasilis Ntziachristos, director of the Unit of Genome and Systems Biology and professor of Biological Imaging at Technische Universität München, is recipient of one of the prizes endowed with 2.5 million euros each of the German Research Foundation.

MARCH 26th
Improvement of tumor radiotherapy: Prof. Dr. Gabriele Machtouff and Dr. Daniela Schilling of the Clinical Cooperation Group “Immune Immunity in Tumor Biology” received a grant of the Wilhelm Sander Foundation endowed with 190,000 euros for the development of new treatment approaches.

MARCH 29th
Development of the microscope of the future: The Federal Ministry of Education and Research promotes the research cooperation “Tech2see” of the Institute of Biological and Medical Imaging of Helmholtz Zentrum München together with ZEISS and Thera Medical GmbH.

APRIL 4th
One hundred mark passed: The Center participates in more than 100 projects within the Seventh Research Framework Programme of the European Union, acquiring more than 50 million euros in third-party funding for this purpose.

APRIL 6th
China Scholarship Award for biologist of the Center: Dr. Jin Zhao of the Institute of Biochemical Plant Pathology is among the 31 German prize winners of the Chinese Government Award for Outstanding Self-financed Students Abroad.

APRIL 10th
Plant researcher in the Top 50: Dr. Klaus Meyer, head of the Research Unit of Genome and Systems Biology of Plants, ranks fourth among the most cited scientists in his field in the field of plant biology.

APRIL 17th
EPSHAN Award 2013 for Dr. Eva Reischl: The deputy head of the research group “Complex Diseases” of the Research Unit of Molecular Epidemiology receives the award of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, which is endowed with 30,000 euros.

APRIL 23rd
Prof. Dr. Bernhard Macháček confirmed as FESTEM president: The head of the platform “Central Isorrganic Analysis” at Helmholtz Zentrum München is elected for the third time as President of the Federation of European Societies on Trace Elements and Minerals (FESTEM).

MAY 1st
Institute of Computational Biology is established: Prof. Dr. Fabian Theis becomes director of the new institute at Helmholtz Zentrum München and also assumes the Chair of Mathematical Models of Biological Systems at Technische Universität München.

MAY 1st
Management expanded: Dr. Alfons Ehrhart takes up his duties as managing director for the scientific-technical infrastructure at Helmholtz Zentrum München.

MAY 9th
Environmental biologist in the Top 50: Prof. Michael Schlöter, head of the Research Unit of Environmental Genomics, is 22nd in the LabJournal ranking of the most cited researchers in the field of microbiology.

MAY 11th
TransAquA is launched: Four institutes of Helmholtz Zentrum München participate in the joint project for the transfer of radionuclides in aquatic ecosystems, which is funded by the Federal Ministry of Education and Research with four million euros.

JUNE 4th
Research supports environmental policy: Prof. Dr. Annette Peters, director of the Institute of Epidemiology II, presents the current status of knowledge on the impact of air pollution on health at the Green Week Conference 2013 in Brussels.

JUNE 21st
Leading virologists in Munich: Upon invitation of the Institute of Virology of Helmholtz Zentrum München and Technische Universität München, the Global Virus Network discusses new insights concerning the fight against virus-associated infectious diseases.

JUNE 25th
Two new junior research groups at the Center: Dr. Janice Mareika Gerdes heads the newly founded junior research group “Primary Cilia and Energy Metabolism” at the Institute of Diabetes and Regeneration Research. At the same time, the research group “Mechanisms of Gene Regulation in T cells” led by Dr. Elke Glaumacher begins work at the Institute of Diabetes and Obesity.

JULY 6th
The 1000+ Award goes to Dr. Bernhard Frankenberger: For a specific immunotherapy against autoimmune diseases and iskemia, the team led by Dr. Bernhard Frankenberger and Prof. Dr. Dolores Schendel at the Institute of Molecular Immunology receives the award of the Bayerische Ministerium für Wirtschaft, which is endowed with 50,000 euros.
Timeline 2013

JULY 1st
Launch of the National Cohort: Prof. Dr. Johanna Wanka, Federal Minister of Education and Research, presents in Berlin the largest German health study with 200,000 participants. Helmholtz Zentrum München is building the new central biorepository on the Neuherberg campus for the National Cohort.

JULY 3rd
Health economists to meet in Munich: Prof. Dr. Reiner Leidl, Institute of Health Economics and Health Care Management, becomes designated chairman of the German Society for Health Economics and organiser of the 6th Annual Meeting of the Society in March 2014 at Ludwig-Maximilians-Universität.

JULY 4th
Decision-making structures profiled: The Supervisory Board of Helmholtz Zentrum München adopts the revised version of the Partnership Agreement and the Rules of Procedure of the Management Board.

JULY 10th
State Prize for two office administrators: Paulina Zangler and Christine Zimmermann are honored for outstanding achievement during their vocational training with the Bavarian State Prize.

JULY 16th
Science Prize of the city of Freising for Dr. Nima Prakash: The scientist at the Institute of Developmental Genetics, together with Prof. Dr. Antonio Simonne, University of Naples, Italy, receives the Science Prize endowed with 20,000 euros for their joint research on Parkinson’s disease.

JULY 19th
Pin of Honor for Georg Gerl: The manager of the Scheyern Experimental Farm in the research alliance Agroecosystems Munich receives the Blue Pin of Honor of Technische Universität München.

JULY 21st
Summer campus 2013 begins: 50 children of staff participate in two-week holiday research program for kids.

AUGUST 1st
Official personal dosimeter service under new management: The physicist Markus Figel takes over the management of Germany’s number one personal dosimeter service, which is located at Helmholtz Zentrum München.

AUGUST 15th
Dissohning protein complexes on the atomic level: At the Institute of Structural Biology under the direction of Dr. Dirk Niessing, a new X-ray crystallography platform is available for drug development.

AUGUST 16th
Ilse Aigner visits Scheyern: In her capacity as Federal Minister for Nutrition, Agriculture and Consumer Protection, the Bavarian politician informs herself at the Experimental Farm of the Center regarding research on the ecological impacts of climate change.

AUGUST 21st
Clinical Research Award for Prof. Dr. Anette-Gabrielle Ziegler: The director of the Institute of Diabetes Research receives the Mary Tyler Moore and S. Robert Levine Excellence in Clinical Research Award of the juvenile Diabetes Research Foundation for her research into new therapies and preventive measures for type 1 diabetes.

SEPTEMBER 2nd
Career start. Accompanied by mentors of the second year of training, 23 young people begin their apprenticeships in one of eight vocational training programs at Helmholtz Zentrum München.

SEPTEMBER 9th
ERC Advanced Grant for Prof. Dr. Magdalena Gütz: The European Research Council (ERC) supports the research of the director of the Institute of Stem Cell Research and chair of Physiological Genomics at Ludwig-Maximilians-Universität with a grant amounting to 2.18 million euros over five years.

SEPTEMBER 14th
New member of Leopoldina: Prof. Dr. Matthias Tschöp, director of the Institute for Diabetes and Obesity, is accepted into the National Academy of Sciences.

SEPTEMBER 16th
Colloquium for Prof. Dr. Rupert Lasser: With a two-day farewell conference, the Institute of Biomathematics and Biometry says goodbye to its founding director.

SEPTEMBER 20th
The Wilhelm Sander Foundation supports therapy approach for lung tumors: Prof. Dr. Reinhard Zoller, Research Unit of Gene Vectors, receives 120,000 euros for his research project.

SEPTEMBER 22nd
Networking with the world’s top scientists: To kick off the Helmholtz-Nature Medicine Diabetes Conference of Helmholtz Zentrum München and the journal Nature Medicine, Prof. Dr. Matthias Tschöp presents the Lifetime Award to Harvard researcher Prof. Dr. C. Ronald Kahn.

SEPTEMBER 25th
Best in Big Data: Claudia AG, a spin-off of Helmholtz Zentrum München, wins the competition of the journal Computerwoche against 18 competitors with a computerized analysis system for stock traders.

SEPTEMBER 27th
Milestone for process organization: Dr. Nikolaus Blum, CFO, and Dr. Uwe Bott, head of Human Resources, inform the staff about the experience and success in implementing a process-oriented organization.

OCTOBER 1st
Oktoberfest Symposium 2013: In cooperation with the German Center for Diabetes Research (DZD), Technische Universität München and the Competence Network Diabetes Mellitus, the Institute of Diabetes Research is inviting participants to a seventh symposium.

OCTOBER 3rd
Winner of the Ernst Schering Prize 2013 is announced: Professor Dr. Magdalena Gütz, director of the Institute of Stem Cell Research at Helmholtz Zentrum München and chair of Physiological Genomics at Ludwig-Maximilians-Universität München, receives the prize, which is endowed with 50,000 euros, for her research on the molecular basis of brain development.

OCTOBER 10th
The Eva and Klaus Grohe Prize goes to Dr. Michael Schindler: For his research in the field of infectious diseases, the scientist of the Institute of Virology receives the prize of the Berlin-Brandenburg Academy of Sciences, which is endowed with 20,000 euros.

OCTOBER 15th
Increased funding for the promotion of young scientists: The junior research group “Molecular Endocrinology”, led by Dr. Nina Uhlenhaut, begins work at the Institute for Diabetes and Obesity.

OCTOBER 17th
German-Chinese cooperation agreement signed: The Institute of Virology at the Beijing Institute of Genomics cooperates in the investigation of the interactions of the hepatitis B virus with its host.

NOVEMBER 16th
Knowledge for all: During the 13th Munich Science Days the Center informs the numerous visitors to the Theresienhöhe about diabetes.

NOVEMBER 25th
Award for new approach to treat Leukaemia: Seven scientists receive the Research Award for Interdisciplinary Cooperation of the Association of Friends and Sponsors (VdFF) of Helmholtz Zentrum München.

NOVEMBER 29th
Further expansion of international cooperation: Managing Director Dr. Alfons Entzen welcomes the Chinese Academy of Sciences during its international visit to Helmholtz Zentrum München.

DECEMBER 3rd
Further expansion of international cooperation: Managing Director Dr. Alfons Entzen welcomes the Chinese Academy of Sciences during its international visit to Helmholtz Zentrum München.
1. Helmholtz Zentrum München achieved outstanding evaluation results in the expert review within the framework of program-oriented funding. What makes us the leading center in the field of environmental health?
Wess: In 2008, under the motto "One 2013", we aimed to become a leading international center in the field of environmental health within five years. The steadily increasing number of high-caliber publications and the comments of many international reviewers, most recently during the POF III review, demonstrate that this aim has been achieved. We received an excellent assessment in the POF III review. What impressed the reviewers besides the top achievements of individual scientists was the interaction between various disciplines under one common topic. Furthermore, we have a good balance between our focus on certain common diseases and technology platforms combined with our expertise in health research and environmental research. With a total of 12 ERC grants, we are the most successful center in the Helmholtz Association.

2. As a vice president, are you responsible for the Research Field Health within the Helmholtz Association? How well is our center anchored thematically in the Helmholtz Association?
Wess: The Center’s profile correlates well with the mission of the Helmholtz Association. Our research activities range from basic research to translational research. Our research topics address the major challenges of the future.

3. Health research at Helmholtz Zentrum München shall ultimately benefit patients. How can we strengthen our translational approach in order to translate research results into medical applications?
Wess: To limit translational research only to translational medicine would be too short-sighted. Of course, as a scientific-technical center we are interested in good collaborations and joint projects with university hospitals because we do not want to have own wards with beds. However, we are keen that our research results benefit patients, as our three translational centers show. But translation involves much more: It includes early-stage drug discovery projects, the search for new biomarkers or even technical equipment for imaging. Another aspect relates to spin-offs. Here, with 18 spin-offs, we have generated several hundred jobs, we are the most successful center in the Helmholtz Association. And finally, we always forget that translation also includes knowledge transfer to society, which can hardly be expressed in the usual statistics. This includes insights into new or improved treatment regimens, as well as findings from environmental research.

4. How are we expanding our endeavors to promote young scientists, now after the successful positioning of the HELENA graduate school?
Wess: One of our great strengths is the promotion of young scientists, now after the successful positioning of the HELENA graduate school. Our HELENA graduate school, established in cooperation with the Technical University of Munich, is internationally established with about 330 PhD students from all over the world. In the years 2011–2014, 123 PhD students have enrolled and so far 35 PhD students have been awarded their PhD degrees. In addition, we have a number of post-doctoral researchers. What impresses us most is the excellent work of our HELENA graduate students. We are keen that our research results benefit patients, as our three translational centers show.

5. Successful research requires motivated researchers. What do we need to offer our scientists to tie them to the Center?
Wess: I see major challenges in the area of mid-level scientists. Here at the Center there is a group of about 200 people, some in management positions and with fixed-term contracts. These are important staff members, without whom our center would not function. It will be crucial to develop new concepts for our personnel and also to find new forms of remuneration, which take performance and function into greater account. A solution is still not in the offing, but the topic must be addressed and receive more attention.

6. What is the greatest challenge facing our center in the next few years?
Wess: Our greatest challenge is the renovation of the infrastructure and its further development. Decades of missed opportunities are now apparent. A few years ago we began a renovation program, using funds of the Center and federal funds from the economic stimulus program, but this was just a drop in the ocean. New laboratory space was leased where we could launch our new activities, and the new diabetes building supported by Bavaria’s Minister President Seehofer helps a lot. But that is not enough to remain internationally competitive. Additional resources are urgently needed.

7. The Center hosts international conferences and events more and more often. What is the objective?
Wess: We follow the recommendations of our Scientific Advisory Board to increase our international visibility through high-level symposia and conferences. Thus, in 2013, the first Helmholtz-Nature Medicine Diabetes Conference took place with the Helmholtz Diabetes Lecture by Ronald C. Kahn and the presentation of the Helmholtz Young Investigators Diabetes Award. Similarly, the already well-established “Oktoberfest Symposium” and the international Munich Lung Conference were held. This year the Center is participating in the Conference of the European Respiratory Society with more than 20,000 attendees, which will also take place in Munich. Unfortunately, we could not in the past and cannot presently host these important events on the Neuherberg campus due to lack of space and infrastructure.
8. Cooperation is central to successful research. How shall we develop our cooperation networks further, also against the backdrop of new forms of cooperation between university and non-university research?

Wess: Technische Universität and Ludwig-Maximilians-Universität are our most important cooperation partners in Munich, and many joint appointments form the backbone of our common endeavors. In the framework of the German Centres for Health Research and a global orientation of the Helmholtz Association and our center, we have also undertaken joint appointments with other locations. With the Karlsruhe Institute of Technology (KIT), and the recently founded Berlin Institute of Health (BIH), interesting new models of collaboration between university and non-university research have emerged. With the BIH, the Federal Government has undertaken a strategic step using considerable resources to strengthen the research location of Berlin. At the present time, the question cannot be answered whether such models are also possible and useful in Munich.

9. We have focused our research on the major common diseases. What shall we focus on in the future?

Wess: In recent years, the Research Field Health has very successfully focused on widespread, common diseases. The founding of the German Centres for Health Research has provided additional impetus. In the framework of this strategic orientation, we are ideally positioned with our center motto “Health and Environment”. It is immediately clear that lung diseases play a prominent role among the environment-related diseases. However, it is also increasingly evident that environmental factors such as diet, lack of physical activity, stress and personal lifestyle play a very important role in diseases such as diabetes. That is why research on these diseases fits perfectly in the Center profile. We were very pleased about the suggestion from the experts of the POF III review to strengthen our activities in the allergy field. We will be glad to take up this suggestion and would like to develop allergy as the third pillar of the Center alongside diabetes and lung diseases. Here the Center is in a unique position because the environmental field can make significant contributions due to its research in the topic of pollen, analysis or microbiome research in the future. And finally, we should not neglect to mention that we play an important role in the field of virus research in the German Center for Infection Research.

10. As part of the POF reviews, we received recommendations. How shall we implement these?

Wess: The POF program was created in science with great support of Program Planning and Management. It must also be implemented in science. Only when it is accepted by the broad basis of scientists it can be successfully implemented with appropriate administrative support. To achieve this, the Board of Directors has developed a strategic plan in coordination with the topic speakers on the basis of recommendations of the Helmholtz Senate. It was discussed and endorsed by the Scientific Advisory Board. This strategic plan was then adopted by the Supervisory Board. In the coming months it will be important to work out the detailed implementation in the topics on a broad basis in science, with the support of Program Planning and Management. It will be important to develop many good ideas to enhance our leading position internationally.

The new governance will help us to achieve this. The Management Committee has a stronger participation of scientists than was formerly the case. Through the participation of the program speaker as well as the topic speakers and the respective scientific coordinators, we can discuss scientific issues much more intensively and then make our decisions.
Dr. Nikolaus Blum, CFO of the Center, served as vice president of the Helmholtz Association until the end of 2012. In that capacity he advocated more flexibility and a de-bureaucratization of scientific structures. In the interview Dr. Blum explains his ideas on the role and development of administrative organizational forms at Helmholtz Zentrum München.

1. Dr. Blum, science at the Center has developed further and at the same time the complexity of the research landscape has increased overall. What challenges for the administration arise from this fact?

2. Science and administration often feel as if they belong to two different worlds. How can this gap be bridged?

Blum: Administration and science are indeed two different worlds. Science is judged on academic performance criteria such as the journal impact factor and the acquisition of external funding. From the administrative side, however, the funding entities expect that the proper execution of administrative processes is ensured. Our task is to bring these two worlds together and thus to create an effective Center. A new approach is the establishment of the Department of Operations and Support, abbreviated OS. With this we wanted to combine the requirements of science and administration as constructively as possible.

3. How must we imagine this?

Blum: Operations and Support has both an interpreter and a support role. It should translate the needs of science into administrative action and at the same time coordinate this action for the purposes of the scientific projects. OS teams are made up of staff members from science and from the administration. A prime example showing the enormous added value of support through OS is when institutes are founded. New institute directors or junior research group leaders must first spend a lot of energy learning how to process procurements, what the hiring procedures are and what possibilities exist for cooperation. With OS, they have a designated contact person who is familiar with the processes and knows how to cope with them.

4. What changes can we expect with the introduction of process-oriented organization?

Blum: Process-oriented organization shall serve to efficiently process the greatly increased number of standard operations. Each year, we hire approximately 800 employees and process 45,000 procurements. With process-oriented organization, the administration has had to cope with the growth process of the Center and at the same time has had to deal with this complexity.

5. In addition to the introduction of OS and process-oriented organization, the administration is continuing to develop its services for science. What concrete measures do you have on your agenda?

Blum: Our catalog of measures is derived consistently from the annual goal for 2014, ranging from improved information and communication to financial processes and personnel matters. Regarding personnel, a policy for fixed-term contracts shall be adopted and implemented this year: Employees with fixed-term contracts shall thus gain more planning security. An applicant management system will be introduced to give the Human Resources Department stronger support in dealing with applicants – that is also a very important point for the public image of the Center. And finally, we will provide the institutes and research units with regular budget information, so that researchers can navigate their resources more easily and efficiently.

6. Since the beginning of 2014 the new governance has been in operation at the Center. To what extent will your core business – research – profit from these new structures?

Blum: The new partnership agreement and the new governance relate primarily to the external management of the Center, i.e. the interaction of shareholders, the Supervisory Board and the Board of Directors. The Public Corporate Governance Code now also applies to the Center. Despite all the changes, we will continue to intensively implement the internal coordination processes. In the Center, the changed governance will result in noticeably increased action and responsiveness. Research will benefit from faster decision making. Today speed is an absolute competitive advantage also in science.
With compliance management, a new internal structure has been created at the Center. What role will it play?
Blum: Compliance means that an organization complies with existing laws and regulations. That is something that is taken for granted. The public and the funding entities expect this from Helmholtz Zentrum München. However, the spectrum of laws and regulations to be observed today is very broad and ranges from legal matters, the annual financial statements, the use of research funds, work safety and IT security to Good Scientific Practice. Compliance management ensures that the framework conditions are known and observed. There are indications of possible vulnerabilities. Compliance management is therefore an aid for all managers, who must ensure that the existing regulations are observed in their area of responsibility.

How can we position ourselves optimally in the international competition to attract the best researchers?
Blum: The attractiveness of the Center for foreign scientists arises primarily from our scientific performance. If this is outstanding, many scientists from other countries will want to come to our center. But of course we must offer the international scientists good conditions and support them in their integration. Here the administration can make an important contribution, by providing contact persons and assistance in finding housing, the appropriate schools or childcare. In the long term we will also raise the issue of personnel marketing to the international level. Against the background of demographic change in Germany, we are dependent on the recruitment of highly qualified foreign employees.

We recruit talent from the outside – how can we promote the potential of staff members at the Center?
Blum: Talent management is one of our most important issues. As a research institution, our primary role is to promote and train young scientists. There are proven instruments for this, such as the Graduate School HELENA or research groups with a tenure track option. But of course the Center must have excellent employees in all its positions. Therefore, our talent management is very broad. Our internal qualification program has grown tremendously in recent years and supports the development of the Center with a number of targeted measures. The offers of the Munich Leadership Program, which we organize for young professionals together with the Centre for Science Management Speyer, and the offers of the Helmholtz Academy are open to employees. Human Resources Development at the Center ensures that the strategic objectives for promoting talent remain in focus.

You successfully advocated more flexible conditions in the recruitment of scientific personnel in the Helmholtz Association. How can we use this new freedom provided by the Academic Freedom Act in the best possible way?
Blum: The Academic Freedom Act has different aims. It affects financial leeway, personnel questions, construction matters and participation options. One of the new possibilities is to carry out construction projects up to a volume of five million euros in each center’s own responsibility, if a corresponding construction controlling exists. We are currently planning to take advantage of this opportunity. We are also planning further measures with regard to personnel.

For years Helmholtz Zentrum München has been committed to improving equal opportunities for women scientists. Has the end of the flagpole been reached?
Blum: Increasing the percentage of women, also and especially in leadership positions, is a declared goal of Helmholtz Zentrum München. A look at the numbers reveals that we have made good progress. We pay great attention to the equal treatment of men and women and use a variety of funding instruments in order to increase the proportion of women in management positions. However, there is certainly potential for more creative measures. In our view, improving the compatibility of work and family plays a key role. The campus kindergarten is already functioning very well. Through the Academic Freedom Act, the Center now has the opportunity to develop further offers of support from its own income. We hope that we can make an additional interesting offer for young families still this year.

What contribution can highly qualified science management make for the international positioning of German health research and in particular research at Helmholtz Zentrum München?
Blum: In today’s complex structures, science is not possible without good science management. It is an essential success factor for modern, interdisciplinary research. Of course, science management has a supporting role and will never replace the originality and creativity of outstanding scientists. However, in national and international competition, the successful implementation of projects, cooperation in networks and in particular, the provision of facilities with the necessary equipment and consumables are no longer possible without qualified research management.
Making the Campus Ready for the Future

1. Dr. Enhsen, your primary objective in your new position is to make the campus fit for the future. What project is at the top of your agenda? Enhsen: My objective is to develop and implement a long-term perspective for the Neuherberg campus. This includes the long-term development of the master plan and parallel to this, the short-term creation and provision of workspace, in particular laboratory space.

2. What is your highest priority for the development of the master plan? Enhsen: We need to develop the campus so that it is flexible and optimally used – now and for future generations of researchers. This means: identification of contaminated sites, renovation, new construction. A number of the buildings and part of the infrastructure date from the late sixties and seventies. Some buildings are no longer worth renovating. These must be decommissioned and deconstructed in order to create new areas for construction. We will retain the core of buildings that can be renovated and expand them for sustainable use. New construction will take place according to modern concepts. Based on the existing buildings, the contamination situation, energy-technical considerations and the usability of the building structure, we must develop the campus so that we can react flexibly to future demands for use.

3. Our center is extensively expanding its diabetes research. Two new diabetes institutes and a new research unit are being established – where will the employees/staff members and laboratories be accommodated? Enhsen: The new Helmholtz Diabetes Campus is in the planning stage. It will encompass two laboratory-office complexes for more than 200 employees respectively and another building on the Helmholtz Pioneer Campus for more than 150 employees. Over the short term we need to lease office and lab space outside of the campus. We have already set up two new diabetes institutes in Garching and the Comprehensive Pneumology Center in Grosshadern.

4. The Helmholtz Pioneer Campus shall provide exceptional young scientists with maximum opportunities for creative research. How will this be reflected in the architecture? Enhsen: In the Helmholtz Pioneer Campus, abbreviated HPC, several scientific disciplines shall work together under one roof. The horizontal and vertical circulation of the building fosters the interaction between the different disciplines and scientists. The HPC will be directly connected to the two new diabetes buildings. Thus, the already existing institutes will have direct contact to the young scientists in the HPC. The architecture will be open and communicative. The young HPC scientists will conduct their research in flexible, large laboratories equipped with state-of-the-art technology.

5. Research thrives on the direct exchange between scientists. What opportunities does our campus, which is close to the Munich city limits, offer for the creation of communicative meeting places? Enhsen: An attractive campus needs facilities for an open exchange at all levels in order to ensure that its central mandate – the transfer of knowledge – is carried out. There is a great need for appropriate space in the Center. In all major remodeling projects and new construction projects, we of course take into consideration the aspects of communication and interaction. The aim is to promote the exchange of ideas and cooperation between the teams. Traffic connections to the Center also play an important role. Good accessibility by public transportation increases the attractiveness of the Center enormously, especially for young scientists and students. In a pilot project with the Munich Public Transport Company, we were able to improve the connections. In the future, however, we want to optimize this further.

6. The Center wants to expand the field of stem cell research. What stands in the way of rapid implementation? Enhsen: Stem cell research at Helmholtz Zentrum München will be located in the future in what is now the Hämatologikum in Grosshadern. The building needs major renovation in various ways, and it will be completely modernized in the coming years during ongoing scientific operations. Unfortunately, we don’t have any alternative space, neither for laboratories nor for infrastructure facilities, so we can’t vacate the building completely during renovation. We therefore have to convert and modernize the building floor by floor.

7. The Center competes for the best talent worldwide. How important are state-of-the-art infrastructure and high-end technology in this competitive situation? Enhsen: To be internationally competitive and to achieve top results, both the scientific environment and the working environment with the buildings, the infrastructure and how well the facilities are equipped with modern technology are essential. The campus is optimally positioned in the science region of Munich. Our task is to modernize the campus and design the working environment in an optimal way to ensure efficiency.
8. From whom can we learn here?
Enhsen: As a rule from the best in the class. We belong to the best in science, but not in infrastructure. Science is developing so fast that the infrastructure can’t keep pace. This problem can be met to some extent by abandoning the use of small-scale lab and office units and instead creating large, flexibly usable work space. But it would be particularly important that we work on the overall project duration and reduce this considerably. At the moment we are trapped in a situation in which we need eight to nine years for a new construction project. The private sector manages to complete a project of the same size and complexity in just two to two and a half years. Of course, projects in the private sector and the public sector cannot be compared one to one. The federal and state governments must be allowed to carry out the test and control mechanisms with the corresponding approval times, since they are working with tax money. But an ambitious goal would at least be to reduce the current project duration times by half and thus strive for a considerable reduction of the financial risk. That would definitely be a success.

9. What role do occupational safety and fire protection play for you?
Enhsen: Occupational safety affects the health of each individual employee as well as his or her colleagues. Nothing should be given higher value. That is why occupational safety measures, including fire protection, are non-negotiable. This is a special task at the Center, since we have a lot of staff turnover among young scientists, PhD students and postdocs. Every year there are 500 to 600 new employees at the Center, who all must be trained in occupational safety and introduced to the work environment. The responsibility for this lies with the institute directors. Our task is to support the institute directors and staff members who have a supervisory role in this endeavor with our expertise. We need to ensure that all employees are familiar with all safety regulations, taking into account that people with many different nationalities and native languages work here. Through annual training modules and regular information, we keep the staff aware of the topic. Fortunately, in addition to the Department of Infrastructure and Safety (ISA) which covers all safety aspects, we have many volunteer safety officers in the institutes. We also have many volunteers in the fire department and hope that in the future staff members will support this important task.

BRIEF PROFILE
DR. DRAZENKA SELESI
As coordinator, Dr. Drazenka Selesi supports the establishment and development of the scientific and technical infrastructure. She works in a team with the Department of Scientific Infrastructure, Technical Safety and Occupational Protection headed by Dr. Alfons Enhsen and the Central Technical Facilities.

10. You have been managing director for the scientific-technical infrastructure in the Center since May 2013. What has impressed you the most?
Enhsen: What impresses me is the science. The progress made here at the Center in recent years seeks its comparison in Germany. Science at the Center plays in the top league. That’s why I very much wish to contribute to the development of the infrastructure, in order to meet the expectations placed in us and to achieve our ambitious goals for the future.
Commitment to Promote the Advancement of Young Scientists

Helmholtz Zentrum München sets standards in the promotion of young scientists. The Helmholtz Graduate School Environmental Health (HELENA) is unique in Europe and is qualifying a new generation of internationally competitive doctoral students. A newly developed postdoctoral fellowship program complements the strategic concept of promoting young talent. The opportunity to be a leader of well-equipped junior research groups offers young scientists from around the world an ideal career springboard.

The Helmholtz Graduate School Environmental Health (HELENA), which was founded in collaboration with Munich’s two elite universities, is internationally recognized as a successful model. It offers doctoral students at Helmholtz Zentrum München an interdisciplinary graduate program within eight thematic fields, which can be tailored to fit each student’s specific interests and needs.

The research focus is on the interaction of individual genetic predisposition, environmental factors and lifestyle and their influence on the pathogenesis of major common diseases. The interdisciplinary training and fostering of social skills and leadership skills shall prepare the doctoral students to assume leadership positions in science and industry. With the Research School Lung Biology and Disease and the Research School of Radiation Sciences, the Helmholtz Association supports its own research school respectively in the fields of lung biology and radiation research under the umbrella of HELENA.

At the end of 2013, in the third year of its existence, the graduate school HELENA had 328 members. The doctoral students belong to 48 different nationalities. Besides Germany and European countries, particularly China is strongly represented.

The postdoctoral fellowship program at Helmholtz Zentrum München was launched in late 2013 with an international call for applicants. Each year, the program recruits ten highly qualified postdocs for three years in full scientific staff positions in the designated thematic fields of the Center. The postdoctoral fellows receive individual mentoring as well as coaching when applying for external funding. The participants in the program are fully integrated into the research environment of their respective institute and are prepared for a successful career in academia or industry.

With its junior research group program, Helmholtz Zentrum München was able to recruit young top researchers from around the world. At the end of 2012 the Center had 14 junior research groups; by the end of 2013 this number had risen to 19. Thirteen of the 19 junior research groups are led by women scientists; seven were funded through Starting Grants of the European Research Council.
Countries of Origin of HELENA Doctoral Students

1. EGYPT  13. HAITI  25. CROATIA  37. SWEDEN
2. ALGERIA  14. INDIA  26. MALAYSIA  38. SERBIA
3. USA  15. IRAQ  27. MACEDONIA  39. SLOVENIA
4. BANGLADESH  16. IRAN  28. MEXICO  40. SPAIN
5. BOLIVIA  17. ISRAEL  29. NEW ZEALAND  41. SOUTH AFRICA
6. BRAZIL  18. ITALY  30. NETHERLANDS  42. TAIWAN
7. UNITED KINGDOM  19. JAPAN  31. AUSTRIA  43. CZECH REPUBLIC
8. CHINA  20. JORDAN  32. PHILIPPINES  44. TURKEY
9. GERMANY  21. CANADA  33. POLAND  45. UKRAINE
10. ECUADOR  22. KENYA  34. PORTUGAL  46. HUNGARY
11. FRANCE  23. COLOMBIA  35. ROMANIA  47. VENEZUELA
12. GREECE  24. KOREA  36. RUSSIA  48. VIETNAM
Three Years of HELENA

Jan Krumsiek’s calendar is as full as that of a successful manager: In January he spent a few weeks again at Weill Cornell Medical College in New York to advance his scientific work. At the same time, he leads his own research team at the Institute of Computational Biology at Helmholtz Zentrum München, supervises four doctoral students and does a lot of work at the computer. In addition, he travels to attend conferences and give lectures. And all this just a year after completing his PhD degree.

The 30-year-old bioinformatician is one of the top young scientists that Helmholtz Zentrum München has promoted in the HELENA Graduate School of Environmental Health. Founded in November 2010, the school is an investment in the future, both for the students and for Helmholtz Zentrum München. “The graduate school provides interdisciplinary education and training in the field of environmental health and is an ideal springboard to a successful career,” said Christian Langebartels, director of HELENA and research director for the field of environmental and radiation research. The spokesperson of the graduate school is Hans-Werner Mewes, director of the Institute of Bioinformatics and Systems Biology.

Jan Krumsiek had already begun his doctoral work when HELENA was founded. He became a member right from the beginning and, according to him, benefited a lot from the HELENA program. In addition to attending lectures in specialized areas, he took advantage of the interdisciplinary courses in presentation training, time and self-management and courses on the steps involved in the publication process. Since HELENA is also an associate member of the graduate school of Technische Universität München, he additionally had the opportunity to take their courses. “I attended a course in project management, which was extremely useful,” he said.

The Thesis Committee, an integral feature of HELENA, offered him guidance for his dissertation and in general for his doctoral work. It is an advisory body, consisting of the individual’s PhD supervisor, another adviser from the Center and an external expert, which motivated him and supported him in strategic questions. “Once a year the doctoral student meets with the Committee and discusses the progress of his/her dissertation,” he said. “That forces you to structure your work and helps you stay focused.” In 2013 Krumsiek was awarded the Helmholtz Doctoral Award in the research field Health.

Krumtsiek’s doctoral project involved processing thousands of metabolic data sets from a study of the KORA platform (Cooperative Health Research in the Region of Augsburg), which is coordinated at Helmholtz Zentrum München. The bioinformatician created correlation analyses between the individual values and depicted them graphically. The result was images of networks which – according to Krumsiek – “actually correspond to biochemical truths. We verified that. What interested me especially about my topic was that in my research group we spanned the spectrum between biology, medicine, mathematics and informatics. From the depths of biology up to programming – everything was included.” Interesting and unexpected conclusions could be drawn from the data: “We were able to visually show that men and women differ greatly in their metabolism of amino acids and fats,” said Krumsiek. “Even differences between depressive and non-depressive individuals or people with asthma and healthy people could be determined.”
And the novel graphical representation enabled yet another application: It provided evidence of metabolic pathways that were not known before. Through the visualization of the network, researchers are now able to assign metabolites to specific chemical processes. On the one hand, this is a contribution to basic research. At the same time, this approach also provides insights for human medicine. The graphical network may help to elucidate diseases through blood tests.

“The success of Jan Krumsiek shows how important it is to provide interdisciplinary education and training for the doctoral students within the framework of HELENA,” said Monika Beer, head of Planning and Management. “They are no longer left to fend for themselves; they can seek advice, plan their careers and network with each other.”

The preparation for professional life is also an important part of the HELENA program. “We invite experts to career seminars to inform the doctoral students about what career options are available in the future,” said Monika Beer. Around 40 percent opt for academic careers; the others go into industry or science management. “We also want to show the young people career paths that are different from the classical paths.” Jan Krumsiek has already decided: He intends to stay at Helmholtz Zentrum München, where he has received a postdoctoral fellowship for three years.

Sibine Bartel is pursuing her doctorate at the Comprehensive Pneumology Center with a dissertation on signaling pathways in the development of asthma. She will finish her doctorate in summer 2014, after a research stay at Children’s National Medical Center in Washington, DC, USA, where she learned a new method to isolate gene fragments. In 2010 she received her Master’s degree in Molecular Biotechnology from Technische Universität München.

“The concept of the Thesis Committee also ensures that the students have mentors and get away from the formerly common individual doctorate. Around 330 graduate students are now taking part in the programs of HELENA, of which 35 percent came from abroad.” Beer said. “China is the most strongly represented, with 50 persons. It is also interesting that more than half of the participants are women.”

“Due to the integration into HELENA and the graduate research school Lung Biology I am linked in a network with other doctoral students. I can participate in conferences in my field, have intensive discussions with visiting scientists at the Institute and thus grow into an international research environment.” Sabine Bartel

“The Center conducts research on important topics and provides an excellent scientific infrastructure. I find the education and training and scientific supervision in the Helmholtz Graduate School Environmental Health to be very enriching. For my scientific work, the KORA studies platform with its well-studied cohorts is particularly relevant. If possible, I would like to remain for some time in Germany after receiving my PhD degree.” Tao Xu

“HELENA was the perfect environment for my doctorate. Through the HELENA graduate program I received a firm basis for my research career, in particular, how to write a good scientific paper.” Dr. Jin Zhao

“HELENA promotes doctoral students not only academically, but also personally in terms of networking, personal development and career planning. I think that’s something special.” Christina Dargel

Tao Xu came to Munich upon recommendation of his Chinese supervisor, Jiao Tong University Shanghai, where Xu completed a Master’s degree in Biostatistics and Bioinformatics... collaborates closely with the Research Unit Molecular Epidemiology at Helmholtz Zentrum München. For his dissertation, Tao Xu is investigating the relationship between metabolic profile, cardiovascular diseases and the influence of smoking. The results of his research have already been published in several international publications (page 12).

Sabine Bartel is a member of the Helmholtz Graduate School Environmental Health and the Medical Graduate Center I of Technische Universität München. At the Institute of Virology she is working on the development of an immunotherapy for the treatment of liver cancer. As spokesperson for the doctoral students, Christina Dargel proposed and supported an event format that provides insight into the day-to-day work of scientists in industry. A former Konrad Adenauer Scholar, she studied biology and pharmaceutical sciences at Munich’s elite universities. She spent one semester at the University of Leiden in conjunction with her Master’s thesis.
As representative for all research programs, in the following pages we present six junior research groups.
Insights into the World of Mitochondria

Cellular “power stations” or mitochondria are Fabiana Perocchi’s passion. The research of the Rome-born scientist revolves around these energy centers of the cells: Mitochondria are the center stage of energy metabolism and are involved in many cellular tasks. Mitochondrial dysfunction can lead to a number of diseases. Fabiana Perocchi investigates the role of mitochondria in cell signaling. Together with her junior research group “Functional Genomics of Mitochondrial Physiology and Pathophysiology” at the Institute of Human Genetics, she is seeking to elucidate the unsolved mysteries of these organelles.

Inconsistencies in scientific models have always fascinated Fabiana Perocchi. “When I discover a puzzle piece that does not seem to fit into the general concepts of a model, I get really excited,” the biologist says. “I keep obsessing about it until I’ve figured out what its function is and how it fits into the context of the whole system.”

Perocchi’s personal puzzle piece is the signaling network of mitochondria. During her time as postdoc at Harvard Medical School she wondered why mitochondria can absorb such a large influx of calcium ions. Perocchi’s curiosity as a researcher was aroused – not least because the answer to this question might provide relevant insights for medical applications. “Knowledge just for knowledge’s sake is not enough for me,” she stresses. “What’s important is that knowledge contributes to improving health.

Perocchi found that the calcium supply in the mitochondria is crucially involved in cell signaling. Because this is disturbed in many common diseases, mitochondrial calcium signaling could provide a promising target for new therapy options. “Once we have precisely characterized calcium regulated pathways in mitochondria, we can then modulate them and develop therapies for diabetes as well as for neurodegenerative and cardiovascular diseases,” Perocchi says. Her team is currently analyzing the effect of various active pharmaceutical ingredients on mitochondrial function in order to subsequently seek new options for future drugs.

From Harvard, Perocchi was attracted to Helmholtz Zentrum München because of the scientific environment. “Munich is a crucible for excellence in the field of mitochondria research. The technological infrastructure and the exchange of ideas with colleagues in related fields have a very positive effect on the advancement of my research,” Perocchi adds. She also greatly appreciates the support of the administrative departments at the Center: “Here I can concentrate completely on my research – I have the feeling that a whole network of departments is behind me.

What Perocchi considers to be most important for her research group is a spirit of cooperation. “Success cannot be achieved if research is conducted in isolation,” she points out.

Everyone in the team must be motivated, curious and independent and at the same time be open to ideas and objections from colleagues. Fabiana Perocchi: “Today research is a dynamic field. Only if you integrate the insights of colleagues into your own considerations can you keep pace with developments and transfer basic research findings into medical applications.”

Fabiana Perocchi’s research interest is intracellular signal transduction with a special focus on mitochondria and their calcium signaling network (image). Mitochondria are critically involved in intracellular signaling.

www.helmholtz-muenchen.de/en/research/research-excellence/portraits-of-researchers/dr-fabiana-perocchi
Peacekeeping Troops of the Immune System against Type 1 Diabetes

Carolin Daniel compares research to studying a mosaic: “If you look at it from a distance, you see a coherent picture. However, viewed up close, in each single mosaic piece you will find another hidden mosaic that first must be elucidated in detail.” For Carolin Daniel and her junior research group “Immunological Tolerance in Type 1 Diabetes” at the Institute of Diabetes Research, the overall mosaic is type 1 diabetes, and the special mosaic piece is the role of regulatory T cells, the so-called peacekeeping troops of the body’s own immune system.

Daniel’s objective is to translate this breakthrough in immunology from the animal model to benefit human patients. Together with her team of five, she is seeking to develop a vaccine that can prevent the onset of type 1 diabetes in childhood.

The disease has a strong genetic component, which is likely triggered by environmental factors. The main trigger, however, is ultimately a false reaction of the immune system in which the produced immune cells do not distinguish between foreign and endogenous components. Normally in such a case, regulatory T cells move to the scene and prevent an attack on the body’s own cells. Daniel therefore refers to the regulatory T cells as the “blue helmets, the peacekeeping troops of the immune system”. However, in type 1 diabetes, sufficient numbers of these “blue helmets” are lacking to carry out this function. The beta cells in the pancreas that produce insulin can be destroyed over a period of time by the pathologically activated immune cells.

Daniel’s therapy concept is to strengthen the peacekeeping troops: It is based on converting naive T cells into regulatory T cells with respect to the specific antigen. In this case, insulin functions as the antigen. That is why researchers first attempted to generate regulatory T cells via stimulation with low doses of insulin. This method proved to be inefficient, and the researchers subsequently used higher doses of insulin. Daniel laughs: “That went according to the motto “more helps more”. In fact, through this method diabetes was partially triggered in the model – but regulatory T cells could not be efficiently produced.”

Instead of quantity, Daniel focused on quality. She developed an insulin variant, which has now been patented, in which a low dose actually leads to the desired result. With her team, the immunologist is now working from an insulin mimetic compound modeled after the natural epitope to develop an equivalent vaccine for humans.

Daniel is convinced that Helmholtz Zentrum München offers her the best conditions to achieve her goal. Here she has access to extensive data and biological samples from children and adults. The material was collected by the director of the Institute of Diabetes Research, Anette-Gabriele Ziegler, in part over a period of 20 years. “The data and samples are a gold mine for research and are essential to develop strategies for the prevention of type 1 diabetes and autoimmunity,” Carolin Daniel points out.
Every day in her practical work, it is clear to Stefanie Eyerich how important it is to develop new therapy options for inflammatory diseases of the skin. “The patients have a very high level of suffering. My goal is to improve their quality of life,” explains the immunologist. Atopic eczema and psoriasis are among the most common diseases of the skin. In Germany around four million people are affected by atopic eczema, most of them children; an additional three million people have psoriasis. An imbalance in the immune system underlies both diseases and leads to the appearance of the symptoms. T cells, which actually fulfill protective functions in the immune system, play an important role in the disease process. T cells, also called T lymphocytes, initiate an immune response in the body as soon as they come into contact with substances that they recognize as foreign. Certain T lymphocytes remember such a specific immune response and when they encounter the same foreign substance at a later time, they trigger a rapid and effective immune response. If the immune system, however, gets out of balance, it classifies the body’s own structures or harmless structures from the environment as dangerous. This leads to an increased release of cytokines, which then trigger allergic and inflammatory reactions.

Together with her team, Stefanie Eyerich analyzes which specific T cells trigger this reaction. The main focus is on the communication factors of the T cells, the cytokines. These interact with epithelial cells in the tissue and instruct them to initiate an inflammatory reaction. The team wants to understand which communication factors are produced so that they can be deactivated with the aid of antibodies. Then, in this case, the command to trigger an inflammatory reaction would not be given. The onset of the disease could be prevented, and the patients could be helped effectively.

“For me it was always important to do research that is medically relevant,” the biologist stresses. The Institute of Allergy Research provides an ideal environment for this: Two colleagues in Eyerich’s team work as doctors in the Clinic for Dermatology and Allergology of Technische Universität München and at the same time conduct research in the laboratory. “We can analyze T cells directly from patient samples and include observations from practice in our research,” says the scientist.

Already during her time as postdoc at Imperial College in London, Eyerich’s primary research interest was immunology and allergy. One of the most valuable experiences she gained from her work there in the large laboratory was “the ‘intensively lived’ interdisciplinary communication”. She found these communication structures again at Helmholtz Zentrum München - another reason “why research here is fun”. From her staff members she also expects “that they are motivated and enjoy doing their tasks”. Stefanie Eyerich herself finds it especially motivating to pass on her knowledge to young team members, in order to develop projects together to lead to success.
Searching for the Origin

His home is always where top scientists collaborate to discover how stem cells develop into the specialized cell types that our body is composed of. Micha Drukker already conducted research on this topic at The Hebrew University in Israel and at Stanford University in the U.S. Since 2012 he has headed the junior research group “Human Pluripotent Stem Cell Lineage Choice” at the Institute of Stem Cell Research at Helmholtz Zentrum München – and feels as if he has arrived home. “I was already acquainted with my colleagues and knew that this is an ideal environment to study fundamental questions and translate the findings for studying development of multifactorial diseases.”

Already as a child, Micha Drukker was fascinated with the question of our own creation: How does a finely coordinated system of organs develop from a single fertilized ovum? How do molecular interactions between organs mediate development? Trying to find the answer to this is what drives Drukker in his research.

The biologist specializes in the study of stem cells. They offer the possibility to study in the lab the development of undifferentiated cells, not yet specified to serve particular functions, into tissues and thus to come closer to solving the question of how we are made to become what we are. Drukker uses two cell types for his research: embryonic stem cells and somatic cells. The latter he reprograms back to their original state, so that they, too, are pluripotent. Then by applying signals and factors they can be instructed to develop into any cell type. Using embryonic stem cells, the scientist defines precisely when pluripotent cells develop into specialized cells and which mechanisms and molecules are responsible for this. “When we have analyzed these processes, we can open up a wide area of medical applications,” says Drukker.

At Stanford University he developed a technique with which tissue progenitor cells can be isolated very efficiently from mixed cultures of differentiating stem cells. Using this technique at Helmholtz Zentrum München, he is now focusing on purifying tissue-regenerating cells from pluripotent stem cells, including beta cells for the therapy of type 1 diabetes patients. “My goal is to replace functionless or inefficiently working cells in diabetes or Parkinson patients with functioning cells,” the scientist explains.

Using the second cell type, the reprogrammed skin cells, Drukker wants to find out how normal pluripotent cells differ from those of the patient samples: “Reprogrammed cells are well suited to study in vitro where the switches are set for the development of multifactorial diseases such as diabetes or neurodegenerative diseases.”

The research group leader also offers expertise and techniques to other scientists. He is convinced that research today can only succeed when the experts of various specialized areas work together in synergy. “The days of the generalists are over,” he stresses. That is why he especially appreciates the fact that a broad scientific spectrum can be encountered directly at the Center. “I work here like in a kibbutz: My colleagues and I are a great community, who are together attempting to understand the question of life emergence. Everyone is at the top of his or her field. That inspires me,” says Drukker.

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The aim of Micha Drukker is to provide cures for diseases by means of induced pluripotent stem cells. His team reprograms cells from patients affected with diabetes and Parkinson’s disease (image) with the aid of mRNA molecules encoding specialized sets of transcription factors.
Proteins under the Hammer

Proteins are the building blocks of life. If something goes wrong during their production, diseases such as diabetes, cancer and neurodegenerative changes can be the result. Using state-of-the-art equipment, Tobias Madl and his ten-member team of the junior research group “Structural Biology of Signal Transduction” are searching for the molecular causes of such production errors.

During his studies, Tobias Madl was also interested in physics, computer science and history. Whether in historical archives or in the chemistry lab – the main objective for the future chemist was to break new ground and to close knowledge gaps. “To have new things to discover and to thus benefit mankind, that’s what drives me forward,” he says, describing his motivation. For him it is important to have the freedom to look right and left. “That is not a waste of time, but rather serves a purpose.”

Tobias Madl’s team is based at the Institute of Structural Biology and the Bavarian NMR Center, which is run jointly by Technische Universität München and Helmholtz Zentrum München. The group maintains close cooperation on various levels. In collaboration with the Institute of Molecular Cancer Research at the University of Utrecht, the researchers explore how signal transductions are influenced by defective proteins and by the environment, e.g. oxidative stress, thus leading to the development of cancer. Together with the Ludwig-Maximilians-Universität München and the German Center for Neurodegenerative Diseases, the role of RNA-binding proteins is analyzed in the regulation of signal transduction. And finally, with partners from the University of Tübingen, the group checks whether the molecular and cell biological findings are confirmed in clinical studies. “These collaborations make it possible to bridge the gap between the disease and the molecular causes,” says Madl, describing the synergy.

Tobias Madl investigates the spatial structures of proteins that transmit signals between cells. He wants to find out how defective proteins transmit signals between cells (in the image transportin), leading to the development of diseases.

To elucidate the interactions between proteins and other cell organelles, different methods must be combined. “I am therefore glad that at Helmholtz Zentrum München there is a great concentration of outstanding biological research. Here I can also study how environmental factors regulate proteins and whether they are responsible for dysregulations”, says Madl. In his opinion, scientific exchange with other research groups is essential to answer these challenging questions. Besides scientific expertise, the research group leader therefore places emphasis on social competence: “We are happy to measure ourselves against external competition. But within the team there is no place for this - we all are dependent on each other and benefit from each other.”
Signals for the Protection of Plants

Corina Vlot-Schuster discovered her fascination with plant immune defense early in her career. During her time at the Boyce Thompson Institute in the U.S. and at the Max Planck Institute for Plant Breeding Research in Cologne, she explored systemic acquired resistance in Arabidopsis thaliana, thale cress. This model plant is also well established at Helmholtz Zentrum München. When she was offered the opportunity to lead the junior research group “Inducible Resistance Signaling” at the Institute of Biochemical Plant Pathology, Vlot-Schuster did not hesitate to accept.

Corina Vlot-Schuster’s area of research is a special form of plant defense called systemic acquired resistance (SAR). Although plants do not produce any antibodies, they can react to locally limited attacks of pathogens with a kind of long-term immunity: Cells die off around the affected area and prevent the spread of the infection. At the same time signal substances are emitted that lead to an increase of resistance in the entire plant and protect against a wide range of pathogens.

This mechanism has been extensively studied in thale cress. Corina Vlot-Schuster showed that SAR also protects barley from invading pests such as bacteria. Together with her six-member team, the Dutch-born scientist wants to characterize the involved signaling molecules in this agriculturally important grain plant and to protect this and other crops against pests in the future with the plant’s natural defense substances. “SAR is very attractive for use in crop agriculture. Since the plant hardly uses resources for this kind of defense, the crop yield is not adversely affected,” explains Vlot-Schuster.

To identify key molecules that are responsible for triggering the mechanism, the plant physiologist is supported by experts from other fields. For the characterization of the signal molecules in barley, she benefited from the work of bioinformaticians in the Research Unit Genome and Systems Biology of Plants: In 2012 they deciphered the entire barley genome. At Helmholtz Zentrum München Vlot-Schuster conducts her research quasi next door to these colleagues: “We are on equal footing, and our collaboration is uncomplicated. We work hand in hand and try to solve problems together.”

This type of collaboration also has a profound effect on her team. Vlot-Schuster selected her staff based on scientific criteria, but also on their social competence. “We discuss all decisions together,” she says. She expects from her team members that they assume responsibility and work independently. Vlot-Schuster: “If you want to be successful in implementing your projects later on, these are core competences.”

The biologist works in a challenging academic environment. “It has become more difficult to publish results in high-quality, prestigious journals”, she observed – a development that she finds also has positive aspects: “You set your own bar higher and higher, and this increases the quality of the research.”

In addition to academic success, however, Corina Vlot-Schuster is also pursuing another objective: “It has always been important to me that my research can also be applied to protect the environment and to produce potentially healthier foods.”

Corina Vlot-Schuster wants to use the natural defense mechanisms of plants for the environmentally friendly production of food crops. Her focus is on signal substances that are involved in systemic acquired resistance (SAR), which she explores in the model plant Arabidopsis thaliana (image) and in barley.
Within the framework of program-oriented funding, Helmholtz Zentrum München is integrated into the two research fields: “Health” and “Earth and Environment”. Following the successful review in the field of Health, the Center is continuing to focus on the investigation of major common diseases. In the third POF phase beginning in 2014, the Center is pooling its resources in the health program GEnCoDe (Genes and Environment in Common Diseases).

In the field of Earth and Environment, the Center is conducting research in the program Terrestrial Environment (TE).

Besides Helmholtz Zentrum München, which coordinates GEnCoDe, the Helmholtz Centre for Environmental Research (UFZ), Leipzig, has a seven percent stake in the project. The scientific content of the program is divided into five topics.

With the program “Genes and Environment in Common Diseases” (GEnCoDe), Helmholtz Zentrum München is assuming a leading role in innovative health research. The aim of GEnCoDe is to elucidate gene-environment interactions and their significance in the pathogenesis of common diseases, in particular diabetes, lung diseases and allergies. The GEnCoDe program is linked beyond the borders of various disciplines. It brings together the successful predecessor programs “Environmental Health” and “Systemic Analysis of Multifactorial Diseases” and generates additional synergies for the elucidation of the underlying mechanisms of major common diseases and their prevention, diagnosis and therapy.

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Helmholtz Zentrum München concentrates its environmental research in the program “Terrestrial Environment” (TE). The Center focuses on the areas of plant defense and stress resistance, water quality, control of ecosystems and the prevention of environment-related diseases.

Helmholtz Zentrum München collaborates closely with the Helmholtz Centre for Environmental Research (UFZ), Leipzig, which coordinates the program, and Forschungszentrum Jülich. With a program share of 23 percent, Helmholtz Zentrum München is engaged in three of the five topics.

In the research area Health, Helmholtz Zentrum München is involved in all cross-disciplinary activities. Helmholtz Zentrum München and four additional Helmholtz health centers have joined together in the association Personalized Medicine. In the research field Earth and the Environment, the Center participates in the cross-disciplinary topics and associations Bioeconomics, Climate Research and Water.
From the publications of the last two years we present 34 scientific highlights.
Brain Signal Regulates Body Weight

Scientists of the Institute for Diabetes and Obesity, in collaboration with partners from the Charité – Universitätsmedizin in Berlin, have discovered that a receptor in the brain whose function was largely unknown until now is involved in the regulation of body weight. As the research group led by Timo Müller has shown for the first time, the molecule Gpr83 (G protein-coupled receptor 83) plays a crucial role in the regulation of energy balance. Thus, mice with a loss of function of this receptor are protected from obesity and diabetes, even after being fed a high-fat diet.

The regulation of body weight is a complex process in which organs such as the gastrointestinal (GI) tract and adipose tissue are in constant cross-talk with the brain about the current energy status. The brain responds to the GI signals with an activation or inhibition of neuronal signaling mechanisms that control the sensation for hunger and satiety. One of these signals is the hormone ghrelin which, produced in the stomach, reaches the brain via the bloodstream. In the brain, ghrelin activates regulatory circuits that control food intake. As the scientists found out, Gpr83 affects energy metabolism both via direct interaction with the ghrelin signaling pathway as well as via not yet identified ghrelin-independent signaling mechanisms. In further studies, specific binding partners of Gpr83 shall be identified.

The researchers thus hope to obtain new strategies for the treatment of obesity and diabetes. If blocking Gpr83 proves to be a safe, targeted approach, this could lead to new pharmacotherapies to treat metabolic diseases.

Ghrelin is a hormone primarily produced in the gastric mucosa that has an appetite-stimulating effect. In the fasting state, ghrelin levels rise in the blood and decrease again after each meal. In addition to the regulation of food intake, ghrelin has a number of other effects such as the stimulation of growth hormone secretion.
Hormones against Metabolic Syndrome

Scientists of the Institute for Diabetes and Obesity together with U.S. cooperation partners have succeeded in using tissue-specific drugs to target metabolic syndrome, a pre-existing condition of type 2 diabetes. They selectively directed estrogen to specific cell types by binding it to the gut hormone GLP-1 (glucagon-like-peptide 1), thereby causing the symptoms of metabolic syndrome to diminish. If the hormone estrogen is chemically conjugated to the gut hormone GLP-1, the estrogen merely passes into the GLP-1 target cells, but not into estrogen-sensitive organs such as the uterus. With this novel conjugate between a peptide and steroid hormone the scientists showed in the animal model that estrogen can maximize the effect of GLP-1 in reducing levels of blood glucose and in loss of body fat, but for the first time without the negative side effects of estrogen on the uterus and without elevated tumor risk. The trick is that the gut hormone only delivers the conjugated estrogen to certain cell types. On the basis of GLP-1, drugs have been developed that are already approved for the treatment of type 2 diabetes. In the animal model, both in the treatment of obesity as well as type 2 diabetes, the novel conjugate shows a significantly better effect than GLP-1 alone. Metabolic syndrome, obesity and type 2 diabetes are increasing in Germany and worldwide in epidemic proportions, thus presenting major challenges to the health system. Therefore new and effective therapy concepts with minimal side effects are urgently needed, especially for these forms of the disease. The conjugate approach may represent a completely new treatment concept which may similarly be applied to a number of other diseases that may likewise be influenced by steroid hormones.

By conjugating the gut hormone GLP-1 with estrogen, scientists succeeded in the animal model to direct this peptide-steroid conjugate to specific tissues. There it caused a reduction of the symptoms of metabolic syndrome without triggering the negative side effects of estrogen.

The metabolic syndrome describes the simultaneous occurrence of multiple disease symptoms such as obesity, elevated fasting glucose and blood lipid levels, and high blood pressure. This combination increases the risk of atherosclerosis, diabetes and heart disease.

Hormone Duo Promotes Loss of Fat Reserves

The interaction of the two hormones glucagon and fibroblast growth factor 21 (FGF21) has a decisive impact on lipid metabolism and body weight. Their coordinated action leads to decreased food intake and increased fat burning, as scientists of the Institute for Diabetes and Obesity in cooperation with the Metabolic Diseases Institute of the University of Cincinnati, USA, discovered. The two neurotransmitters are thus considered to be promising target structures for treating obesity and type 2 diabetes. As “hunger hormone”, glucagon mediates a reduction of the energy reserves of the body. For the first time, the scientists found that the direct interaction with the neurotransmitter FGF21 is required for this effect. The team led by Kerstin Stemmer and Matthias Tschöp studied the long-term effect of glucagon in a mouse model and showed that this effect is characterized by decreased food intake, increased fat burning and decreasing cholesterol levels. At the same time there was a significant increase in the hormone FGF21. This effect could be detected not only in mice but also in humans. If the mice lacked FGF21 due to a genetic defect (FGF21 knock-out mice), glucagon lost its positive properties on metabolism. From this the scientists infer that FGF21 is essential for the effects mediated by glucagon on fat burning and cholesterol levels. The results support earlier work by the team according to which fusion hormones from glucagon and glucagon-like peptides (e.g. glucagon-like-peptide 1, GLP-1) have a significant potential for the treatment of obesity and diabetes. Until now, however, the signaling pathway was unknown through which glucagon reduces fat reserves. In further studies the details of the hormonal interaction of glucagon and FGF21 shall be explored to examine potential applications for the treatment of metabolic diseases.

Due to the coordinated action of the two hormones glucagon and fibroblast growth factor 21 (FGF21), there is a decreased food intake and increased fat burning. Therefore, the two substances are considered to be potential targets for the treatment of metabolic diseases such as obesity and type 2 diabetes.

The main task of the peptide hormone glucagon, which is formed in the alpha islet cells of the pancreas, is to increase the blood glucose level. When blood glucose levels drop, glucagon is released into the blood stream and is the counter-regulatory hormone opposing insulin action in glucose and lipid metabolism.


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BRIEF PROFILE

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2002-2003: Guest scientist at the Woodruff/Selley Obesity Research Laboratory, Metabolic Diseases Institute, University of Cincinnati, USA

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2008-2010: Scientific staff member, Max Delbrück Center for Molecular Medicine Berlin and German Institute of Human Nutrition, Potsdam-Rehbrücke

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2013: PhD degree
**Efficacy Prognosis for Gastric Bypass**

Gastric bypass is one of the most frequently performed surgical procedures used to treat obesity and leads to a rapid loss of body weight in most patients. In addition, the surgical intervention induces an improved glucose metabolism – even before the weight loss. These metabolic improvements, however, vary considerably from patient to patient. A hormone test could possibly predict to what extent a gastric bypass would improve metabolism. Scientists led by Matthias Tschöp of the Institute for Diabetes and Obesity at Helmholtz Zentrum München and Kirr Habecker at the Metabolic Disease Institute of the University of Cincinnati discovered this using an animal model. After gastric bypass surgery the concentration of the gut hormone GLP-1 (glucagon-like-peptide 1) in the blood rises significantly. GLP-1 increases insulin secretion and contributes to improved blood glucose levels and blood lipids. As the scientists led by Tschöp and Habecker showed, the efficacy of the secreted GLP-1 on blood glucose levels varies: the higher the sensitivity of the rats in the animal model to GLP-1, the more effective the gastric bypass. GLP-1 sensitivity could thus serve as a new predictive biomarker for personalized therapeutic approaches for type 2 diabetes and obesity. If the results are confirmed in the patient trials, the hormone response could be tested prior to a planned gastric bypass to determine to what extent the patient would benefit from the surgical procedure.


**Evolution of Energy Metabolism**

The response to the hormone GLP-1 (glucagon-like-peptide 1), which is formed in the gastrointestinal tract, can predict the efficacy of a gastric bypass. GLP-1 sensitivity could therefore be used as a new biomarker for personalized therapeutic approaches in patients with type 2 diabetes and obesity.

In a gastric bypass, only a small remnant of the stomach that holds about 15 ml remains. Furthermore, the upper small intestine is bypassed. The digestive juices are introduced into the deeper portions of the intestine where digestion begins. As a result, only part of the food is absorbed. The undigested food is conveyed into the large intestine.

Brown adipose tissue is a special form of fat tissue, whose cells are able to generate heat by oxidation of fatty acids (thermogenesis). This occurs in numerous mitochondria, which are also responsible for the yellow-brownish color of the tissue.


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**Original Publication:**
Biomarkers of Pre-diabetes

Pre-diabetes is the early form of type 2 diabetes, one of the most important common diseases. Between about eight to ten percent of the German population suffers from this disease, and its incidence is increasing rapidly. In the pre-diabetic stage, the further development of the disease can be largely prevented, for example by dietary changes or increased physical activity. Up to now, however, no specific biomarkers have been available to reliably detect pre-diabetes.

In an interdisciplinary study led by Rui Wang-Sattler, scientists of the Research Unit Molecular Epidemiology, in collaboration with researchers from the Institutes of Structural Biology, Human Genetics, Experimental Genetics, Epidemiology II, the Genome Analysis Center and from partner institutes in the German Center for Diabetes Research identified three candidate biomarkers for pre-diabetes, two of which predicted the risk of the disease in individuals. Using a metabolomics approach, they quantified 140 metabolites in 4297 serum samples of the population-based Cooperative Health Research in the Region of Augsburg (KORA) cohort. The results were independently confirmed from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study.

As the concentration of the biomarkers in blood are indicative of pre-diabetes, this study suggests that preventive measures can be taken. The three metabolites are glycine, acetylcarnitine C2 and lysophosphatidylcholine (LPC) 18:2.

Metabolomics studies have revealed that three metabolites are candidate biomarkers for pre-diabetes – an early form of type 2 diabetes. With the aid of these biomarkers, the disease can be detected soon enough to halt or even prevent its development.

Metabolomics is the systematic study of the small-molecule metabolite profiles of an organism. The analysis is performed by means of mass spectrometry or using an NMR spectrometry.

Three candidate biomarkers for pre-diabetes associated with seven type 2 diabetes-related genes.
Role of Genetics in Type 2 Diabetes Pathogenesis

Genome-wide association studies (GWAS) are an effective method to detect genetic variations that play a role in the pathogenesis of diabetes mellitus. These may help identify individuals at an early stage that have an increased risk of diabetes. Epidemiologists at Helmholtz Zentrum München therefore also participate in international research consortia such as DIAbetes Genetics Replication and Meta-analysis (DIAGRAM), the Glucose and Insulin-related Traits Consortium, which investigate the genetic causes of diabetes by means of GWAS, among other methods. In the consortia, the genetic association analyses are centrally coordinated to identify and specify gene variants with reference to type 2 diabetes and related metabolic disorders.

Through meta-analyses with large numbers of individuals, 53 gene loci that impact blood glucose levels were discovered or earlier findings were confirmed; 10 gene loci associated with type 2 diabetes were identified for the first time.

In genome-wide association studies (GWAS), state-of-the-art analysis techniques are used to detect genetic differences between healthy subjects and people with diseases such as diabetes mellitus. Thus, associations between genetic alterations and external characteristics can be detected, and genetic risk factors for the development and/or course of the disease can be identified.

Relationship between PTSD and Type 2 Diabetes

People who suffer posttraumatic stress disorder (PTSD) have a significant risk of developing type 2 diabetes. PTSD is an adjustment disorder after experiencing a trauma and leads to massive stress symptoms. An association between stress due to mental illness and diabetes has been discussed for a long time. Now for the first time, Karoline Lukašek of the Institute of Epidemiology II at Helmholtz Zentrum München and Johannes Kruse of the Clinic for Psychosomatic Medicine and Psychotherapy at the University Hospital Giessen/ Marburg and colleagues have demonstrated a clear association between the two diseases. The scientists analyzed the data of the population-based cohort study and administered a glucose tolerance test. In the cohort, a total of 50 people with PTSD were identified. 48% of the KORA participants who had manifest type 2 diabetes, and additionally 33% showed signs of pre-diabetic metabolic state, a pre-form of diabetes. The evaluation of the data revealed a significant association of PTSD with type 2 diabetes; however, a higher incidence of pre-diabetes related to psychological stress was not observed. The scientists assume that the chronic stress burden of PTSD patients leads to adjustments in the hormonal reaction patterns. This can have a pathological impact on the metabolism and the utilization of glucose. Elucidating the association between psychological factors and metabolic disorders will therefore be an important task of diabetes research in the future.

According to the scientists, the treatment of metabolic risk factors should already be part of the therapy for patients with PTSD and other mental illnesses.
Breastfeeding is healthy — this is true not only for the baby, but apparently also for the mother. If she develops gestational diabetes during pregnancy, she can reduce her risk of developing type 2 diabetes by about 40 percent through breastfeeding. Gestational diabetes is a metabolic disorder limited to pregnancy that increases the risk of developing type 2 diabetes after delivery. Impaired insulin release and reduced insulin sensitivity result in this metabolic disorder characterized by elevated blood glucose levels. Women who had to be treated with insulin during pregnancy bear the greatest type 2 diabetes risk: Almost two thirds of this group of participants of a gestational diabetes study developed type 2 diabetes within three years after delivery; within 15 years even more than 90 percent developed type 2 diabetes postpartum. Previous studies reported a short-term positive effect of breastfeeding on the metabolism of the mother. These studies indicate that breastfeeding for one to three months improves lipid and glucose metabolism and reduces estrogen levels during that time. Apparently even three years after birth, breastfeeding influences the concentration of two hormones that control hunger and satiety: the appetite-stimulating hormone ghrelin and the hormone PYY, which mediates a feeling of satiety. The novelty of this study presented here is the finding that breastfeeding prevents type 2 diabetes in the mother even over the long term. According to the findings of the Institute of Diabetes Research, the duration of breastfeeding is crucial: Only those who breastfed for more than three months had a 15-year risk of 42 percent of developing type 2 diabetes compared to 72 percent in mothers who breastfed less than 3 months. The test subjects were able to reduce their diabetes risk even more if they fed their baby during this period exclusively with breast milk (15-year risk of 34.8 percent). By breastfeeding, the participants were able to delay the development of type 2 diabetes by an average of ten years. Now the aim of the research group led by Anette-Gabriele Ziegler is to investigate the mechanisms that are responsible for this long-term effect of breastfeeding.
Air Pollution Promotes Insulin Resistance

Airborne pollutants play an important role in the development of chronic diseases of the respiratory and cardiovascular systems; for diabetes, however, no reliable data has been available until now. Elisabeth Thiering and Joachim Heinrich of the Institute of Epidemiology I conducted a study on children to determine a possible association of air pollution and insulin resistance, a precursor of type 2 diabetes. They evaluated blood samples and data from 397 10-year-old children of a prospective cohort study. For all residential addresses of the children since their birth, the respective traffic-related air pollutant concentrations of particulate matter and nitrogen dioxide (NO2) were modeled and related to insulin resistance at the age of ten years. The socio-economic status of the families, the children’s exposure to passive smoking and their birth weight, developmental status and body mass index (BMI) were taken into account. The statistical analyses revealed that levels of insulin resistance were greater in children with higher exposure to particulate air pollution and nitrogen dioxide. Per 10.6 μg/m3 additional NO2 content in the air, the incidence of insulin resistance increased by 17 percent. Also the distance of the residence to roads with heavy traffic was significant: Near to busy roads the insulin resistance increased by seven percent per 500 meters. These relationships were independent of confounding factors such as socio-economic status, passive smoking, or BMI. Air pollutants are potential oxidants and can oxidize lipids and proteins directly or activate oxidizing signaling pathways. This oxidative stress may be an explanation for the development of insulin resistance due to traffic-related air pollutants. In the follow-up observation of the cohorts, the researchers are now investigating whether their observations also apply to older children and whether e.g. a change of residence with altered particulate pollution allows conclusions about the significance of exposure in early childhood and then later on. Currently, the clinical relevance of an increased risk of insulin resistance caused by particulate matter cannot be assessed. However, the results support the hypothesis that the development of diabetes in adulthood is related to environmental factors earlier in life.

Type 1 Diabetes Is Predicted by Autoantibodies

The autoimmune disease type 1 diabetes often manifests during childhood and adolescence. Characteristic markers of the disease are autoantibodies – i.e. immunoglobulins directed against the body’s own components. They appear when insulin producing cells in the pancreas are destroyed and may be present in the young patient’s blood already at the age of six months to three years. In a 20-year period after the first appearance of so-called multiple autoantibodies – sooner or later depending on the presence of certain risk factors – the disease manifests. In order to determine the progression rate more precisely, scientists from the Institute of Diabetes Research compared the data from their own studies (BABYDIET and BABYDIAB) with the data of two other prospective cohort studies (DAISY from Colorado and DIPP from Finland). Overall, they were able to analyze the results of 13 377 children over a period of 20 years, making this study the largest of its kind in the world. Anette-Gabriele Ziegler and Christiane Winkler of the Institute of Diabetes Research and their colleagues from international cooperative projects found that 70 percent of children who have more than one type of autoantibodies against islet cells in the pancreas develop type 1 diabetes within ten years. Over a period of 15 or 20 years, the percentage of children is even 85 percent or almost 100 percent. Subjects with only one type of autoantibodies, however, develop type 1 diabetes only in 15 percent of the cases within ten years, and children without autoantibodies almost never develop type 1 diabetes. These results show that the development of type 1 diabetes is usually predictable. Therefore, the detection of autoantibodies provides a relatively simple and cost-effective way to diagnose type 1 diabetes at an early stage and, if applicable, in time to begin preventive and therapeutic measures.

In type 1 diabetes, characteristic autoantibodies against islet cell antigens often appear quite early in the blood of young patients. Through the detection of multiple autoantibodies, the disease can often be diagnosed in the preclinical stage.

The insulin resistance syndrome – also known as the metabolic syndrome – refers to the common occurrence of several symptoms or diseases: obesity, elevated fasting blood glucose and blood lipid levels and high blood pressure. This so-called metabolic syndrome increases the risk of atherosclerosis, diabetes and heart disease.
Progression of Type 1 Diabetes

Type 1 diabetes is an autoimmune disease. Just how quickly the autoimmune process progresses and type 1 diabetes develops appears to be dependent on an interplay of genetic and environmental factors. Scientists of the Institute of Diabetes Research have partly succeeded in elucidating relevant gene combinations. The researchers led by Peter Achenbach and Anette-Gabriele Ziegler analyzed data of the BABYDIAB study. This prospective cohort study includes participants from birth on who have at least one relative with type 1 diabetes. Two extreme groups were compared with each other over an observation period of 20 years: the group of slow progressors – children who developed type 1 diabetes at the earliest ten years after the first appearance of autoantibodies – and the group of rapid progressors – children who developed the disease at the latest three years after their first appearance. Basically, as far as demographic factors were concerned, the children were comparable. With respect to environmental factors they differed only in the factors spontaneous delivery or cesarean section. While half of the rapid progressors were delivered by cesarean section, this was the case with only every sixth slow progressor. The greatest immunological difference was seen in the development of autoantibodies against insulinoma-associated antigen-2 (IA-2A), which in general indicate a high diabetes risk. The slow progressors showed a delayed development of IA-2A. Characteristic of the rapid progressors was a higher percentage of risk variants of genes involved in immune regulation. These gene variants are individually connected to a relatively small increased risk of disease. However, if they occur in certain combinations, this seems to favor an early onset of the disease. This is especially true for genes encoding for interleukin-2 receptor (IL2), the alpha subunit of the IL-2 receptor (CD25), interleukin-10 and interferon-induced IFIH1 helicase. In contrast, no difference could be found regarding the HLA (human leucocyte antigen) gene variants that pose the greatest risk for type 1 diabetes.

The development of type 1 diabetes may take only a few months, but also many years. A combination of specific risk gene variants, the early appearance of autoantibodies against the insulinoma-associated antigen-2 (IA-2A) and a birth by cesarean section seem to facilitate a rapid progression of the autoimmune disease.

Infections Increase Type 1 Diabetes Risk

Infections in the first months of life predispose to the later presence of autoantibodies, which are responsible for the development of type 1 diabetes. In particular, respiratory diseases in the first year of life, especially an acute common cold (nasopharyngitis) appear to play an important role.

Type 1 diabetes is the most common metabolic disease in childhood and adolescence. The body’s immune system attacks the insulin-producing cells in the pancreas and destroys them. This autoimmunity, which underlies the metabolic disorder, is based on a genetic predisposition and is influenced by environmental factors. Type 1 diabetes can occur at any age. The peak incidence is during puberty from age 10 to 15 years.

Islet autoimmunity refers to the presence of autoantibodies against insulin-producing beta cells of the pancreas. It is characteristic of type 1 diabetes and most commonly appears between the ages of six months to three years. Scientists at the Institute of Diabetes Research have investigated whether in this phase of life infectious agents might be considered a potential trigger for the dysregulation of the immune system. They analyzed the data of children of the BABYDIAB study who have relatives with type 1 diabetes and thus an increased risk for islet autoimmunity. The parents kept a log of the infections occurring in the first three years of life of the children — differentiated according to respiratory tract, gastrointestinal tract and other infections. Fever and medication were also recorded and the blood of the children was regularly analyzed for autoantibodies.

In the first year of life an association between respiratory infections and the presence of islet autoantibodies was observed — especially with infections of the upper respiratory tract such as nasopharyngitis (the common cold). Children with islet autoantibodies were infected at least twice in the first year, mainly with pathogens of the respiratory tract. Children who had more than five respiratory infections in the first year had the highest risk of islet autoimmunity. The scientists suspect, however, that the increase in autoimmune risk is not caused by a specific virus but rather by the sum of infections and the thus released inflammatory cytokines. According to the principal investigator of the study, Anette-Gabriele Ziegler, and her colleagues, frequent respiratory infections in the first year of life represent a possible risk factor for type 1 diabetes. In genetically disposed risk children, multiple episodes of colds in early childhood should be avoided if at all possible, and vaccinations or anti-inflammatory therapies should be taken into consideration as preventive measures against type 1 diabetes.


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Interplay of Cytokines in Asthma

The cytokine interleukin-22 may control the extent of asthmatic lung inflammation, according to a study by an international research team. The analysis of T-helper cells derived from the lungs of patients with asthma detected the presence of the T-helper cell type Th22, which was originally described in the skin. Interestingly, however, the lead cytokine of the Th22 cells, interleukin (IL)-22, was co-produced in a number of T cells with gamma interferon (IFN-γ). IFN-γ is considered to be pro-inflammatory because, among other things, it stimulates the production of adhesion molecules in epithelial cells, while interleukin-22 has the opposite effect – it promotes defense mechanisms and wound healing. In an in vitro model using human bronchial epithelial cells, the researchers examined the interaction of the two substances and demonstrated that IL-22 and IFN-γ are apparently antagonists. In the presence of IFN-γ, IL-22 cannot fully develop its positive characteristics, and this leads to diminished wound healing responses. On the other hand, however, IL-22 also suppresses the pro-inflammatory effect of IFN-γ in the inflammatory process. The results suggest that the therapeutic administration of interleukin-22 or measures that support its production could reduce the acute inflammatory response in asthma. However, this protein is ambivalent in its effect. Too much IL-22 can lead to excessive proliferation of epithelial cells, a phenomenon that is e.g. observed in psoriasis. In addition, IL-22 interacts strongly with other interleukins, and these interactions are not yet sufficiently understood. As next step the scientists therefore want to study the interaction of IL-22 and IFN-γ in the mouse model.

Scientists at the Center of Allergy and Environment (ZAUM) of Helmholtz Zentrum München and Technische Universität München investigated the anti-inflammatory role of interferon-22 in allergic asthma in the framework of an international research group.

Both interleukins (IL-x) and interferons belong to the family of cytokines. They are endogenous tissue hormones, which act as communication factors between immune and tissue cells.

More Risk Genes for Allergies

In a meta-analysis of several genome studies an international team of scientists has identified ten genes that are involved in the development of allergic sensitization. In the genome-wide association studies (GWAS), the scientists correlated the genetic profile of the study participants with the presence of specific IgE antibodies. They found that ten loci are involved in a total of 25 percent of all allergic sensitizations, the immunological process in which antibodies form against allergens, which are actually harmless substances in the environment. These antibodies subsequently cause the allergic symptoms. The researchers analyzed data from more than 10,000 people with allergic sensitization and approximately 20,000 control subjects. Among them, were participants of the German birth cohorts GINIplus and LISAplus; their evaluation was carried out by Marie Standl and Joachim Heinrich of the Institute of Epidemiology I. This comprehensive genetic analysis in relation to the objective measurement of allergic sensitization enables an assessment of the identified genes as risk factors for allergic diseases. In addition, all of these genes showed a correlation with the occurrence of allergic manifestations such as hay fever and asthma. The results of this meta-analysis indicate that enormous genetic diversity underlies allergic diseases.

Allergic diseases are increasing throughout the world. In Europe alone an estimated 80 million people are affected. The reason for the allergic reaction is a complex gene-environment interaction.
Cost of Medical Care in Early Stages of COPD

Scientists of the Institute of Health Economics and Health Care Management at Helmholtz Zentrum München have investigated the association between early stages of COPD and the utilization of medical care. The researchers based their investigation on the KORA study comprising more than 2000 participants between 40 and 90 years of age. They compared their costs for medical care to the doctor, hospital stays and medications. Based on the results, the researchers conclude that suitable preventive measures are needed for COPD not only from a medical perspective but also from an economic perspective to keep the disease from progressing to a more advanced stage. First and foremost, this means that smokers who already have COPD are motivated to stop smoking, since smoking cessation is one of the most effective interventions to slow the worsening of the disease.

By means of a pulmonary function test they identified test subjects with reduced lung function and classified them into mild (Stage I) or moderate (Stage II) COPD. In computer-assisted interviews using detailed questionnaires, participants were asked about their visits to the doctor, hospital stays and medications. From this data, their costs for medical care were derived. Then the researchers compared the calculated costs between participants with and without COPD taking age, sex and level of education into account. The results show that people with early stage (I) COPD do not cause substantially higher costs for medical treatment than participants without the disease. However, as soon as the moderate stage is reached, costs increase and are on average 990 euros higher per year for people with COPD compared to people with normal lung function. In view of the high incidence of COPD, this means that alone for the treatment of this stage, annual costs of about two billion euros are incurred for the German health care system. The total costs of COPD are many times higher, especially when patients in stages III and IV are included in the cost calculation. In order to quantify these costs as well, the research group collaborates within the Competence Network COPD, where information from 2700 patients across Germany is being collected and analyzed. So far, from these results, the researchers conclude that suitable preventive measures are needed for COPD not only from a medical perspective but also from an economic perspective to keep the disease from progressing to a more advanced stage. First and foremost, this means that smokers who already suffer from mild COPD should be motivated to stop smoking, since smoking cessation is one of the most effective interventions to slow the worsening of the disease.

Comparison of the frequency of outpatient visits, hospital stays and use of medication between healthy individuals and subjects with COPD in the mild stage (I) or moderate stage (II). The resulting costs were estimated, taking into account age, sex and level of education.

People who suffer from a moderate form of COPD cause around 990 euros higher medical costs due to illness per year than comparable individuals who do not have the disease. For the treatment of this disease stage alone, this means annual costs of about two billion euros for the German healthcare system. Therefore preventive measures are needed to stop the development and progression of COPD.

COPD stands for chronic obstructive pulmonary disease; it is caused by a chronic inflammatory pulmonary disorder that leads to the narrowing of the small airways. It occurs primarily in smokers and is often accompanied by coughing, excessive mucus production and breathlessness.
Key to Neurogenesis

The formation of nerve cells is mainly restricted in mammals to the development phase and takes place in the adult stage only in a few regions of the forebrain. The usual case in the adult brain is the formation of supporting cells, also called glial cells. In fact, even stem cells that were transplanted as a therapy for neurodegenerative diseases usually develop into glial cells instead of the desired neurons. The few regions of adult neurogenesis offer an opportunity to investigate just how neurons can be formed even in the adult brain. Both in the developing brain and in the adult brain numerous transcription factors are involved in neurogenesis. However, it is still unclear how the final differentiation of the progenitor cells is controlled at the molecular level.

One key mechanism in this process was elucidated by the team led by Jovica Ninkovic and Magdalena Götz of the Institute of Stem Cell Research. By searching for the interaction partners of the transcription factor Pax6, which plays a major role both in the development of the brain and in adult neurogenesis, the scientists showed that Pax6 interacts with the so-called BAF complex, which can alter the chromatin structure, and that this interaction determines the fate of the neural progenitor cells. Through the interaction, the chromatin is modified in such a way that certain genes that serve the regulation of neuronal differentiation become accessible. As a result, the genes necessary for neuronal differentiation are more strongly expressed and the fates of neuronal cells – even in surroundings where otherwise only glial cells are formed – are stabilized. A loss of function of Pax6 or BAF – depending on the surroundings – leads to the formation of glial cells instead of neurons. Thus, the scientists describe for the first time certain molecular prerequisites of neurogenesis in the adult brain. This could be the basis for new therapies, e.g. to stimulate the formation of nerve cells in neurodegenerative diseases or after brain injuries and to replace damaged cells.
Oligodendrocytes are cells of the central nervous system that enable nerve cells to efficiently conduct electrical signals. Scientists of the Institute of Stem Cell Research have now gained new insights into the origin and development of oligodendrocytes, which may play an important role in multiple sclerosis.

Oligodendrocytes are cells of the central nervous system that produce the myelin sheath, a lipidous biomembrane which coats the axons of nerve cells to provide insulation that allows electrical signals to propagate more efficiently. This insulation is necessary in order to ensure a rapid nerve conduction velocity.

In some neurological diseases and in particular in multiple sclerosis, the immune system destroys the myelin. As recent studies have shown, depending on their location in the brain, oligodendrocytes can regenerate throughout life from oligodendrocyte progenitor cells. The team led by Leda Dimou has now taken a closer look at these oligodendrocyte progenitor cells to identify the reason for these differences in their differentiation potential.

Depending on the brain region in which the progenitor cells are located, a smaller or greater quantity of oligodendrocytes is generated which can produce myelin. Progenitor cells in the white matter develop in both brain regions into myelin-producing oligodendrocytes. Progenitor cells from the gray matter are less effective. The next step for the researchers will be to identify the factors which determine the effectiveness of these oligodendrocyte progenitor cells. Their goal is to define conditions in which these progenitors will always differentiate into oligodendrocytes that form myelin. Even though a therapy for multiple sclerosis still appears to be far in the distance, this research is an important contribution to understanding the origin and course of such neurological diseases.

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system and is caused by demyelination of the nerves in which the body's own immune cells attack the myelin sheaths of the nerve axons. The cause of this autoimmune reaction is not yet fully understood. MS is one of the most common neurological diseases in young adults. To date, no cure has been found.

An efficient method for the rapid production of mouse disease models has been developed at Helmholtz Zentrum München. Mouse models are used for the genetic analysis of disease mechanisms and are still considered to be indispensable for this purpose. In most cases, models are used which are produced by targeted mutations in embryonic stem cells (ES cells). However, this production process is complex and time-consuming, since among other steps, targeting vectors must be constructed with selection markers, mutated ES cells must be isolated and germline chimeras must be produced. All of these procedures are very laborious and time intensive. Including all steps, the scientists often need one to two years to produce a knockout mouse model using these methods. This poses a hurdle for the analysis of the ever-increasing number of known human disease-associated mutations that are discovered using high-throughput analyses of the human genome. Scientists of the Institute of Developmental Genetics have succeeded in developing a faster way to produce mouse disease models. By microinjection of so-called TALENs (Transcription Activator-like Effector Nucleases) and synthetic oligodeoxynucleotides directly into the embryos in the one-cell stage, any desired mutation or deletion can be induced within two days and can also be reversed. Since for this purpose neither ES cultures nor targeting vectors are required, this technology enables immediate changes in the germ cells, so that heterozygous mutants are available within 18 weeks. This novel method is thus significantly faster than the previously used methods. Through the intelligent production of mouse models required for drug development, the number of experimental animals needed for this purpose can be drastically reduced.

By microinjection of TALENs and synthetic oligodeoxynucleotides, the scientists altered the genes in the fertilized egg cells of mice so that all progeny cells were equipped with the same mutation. Because through this method the laborious steps to produce targeted mutants are not required, animal models can be established much faster and using substantially fewer experimental animals.


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HIGHLIGHTS 2012/2013

Oligodendrocytes and Multiple Sclerosis

Faster Production of Disease Models


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Human Glial Cells Can Be Reprogrammed

The regeneration of functional neurons is an innovative approach to the therapy of neurodegenerative diseases such as Alzheimer’s disease or stroke. In the adult mammalian brain, however, most areas no longer contain neuronal stem cells or progenitor cells from which new neurons could be formed. Several years ago, members of the Institute of Stem Cell Research headed by Magdalena Götz showed in a mouse model that by selective transfer of individual transcription factors it is possible to reprogram glial cells – i.e. supporting cells with multiple functions – to nerve cells. Transcription factors are regulatory proteins that control which genes are active or inactive in the cells. Now a research team led by Magdalena Götz and Benedikt Berninger has succeeded in proving that the animal experimental approach is also applicable to human glial cells. Using specimens derived from the surgery of adult epilepsy patients, Marisa Karow and her colleagues showed that specific cells of the cerebral cortex (cells derived from pericytes) can be reprogrammed into neurons through the retrovirus-mediated expression of the two transcription factors Sox2 and Mash1. These induced neurons fire action potentials and form networks with other neurons; thus, they are able to integrate themselves into neuronal networks. This shows for the first time that there are cells in the adult brain which can be directly reprogrammed into functional neurons for therapy purposes – without having to take a detour via pluripotent cells. On the basis of this knowledge, researchers are seeking active agents to activate the reprogramming of glial cells in patients with neurodegenerative diseases or brain traumas and thus to initiate a self-healing process in the injured areas of the brain.

For the first time the formation of new nerve cells from somatic cells of the human brain has succeeded: Specific cells of the adult human cerebral cortex could be reprogrammed into functioning neurons with the aid of two transcription factors.

The brain consists of two main types of cells: the neurons, which transmit information, and the glial cells, which have a supporting function and are involved in the metabolism of the brain. In many degenerative diseases of the brain – stroke, Alzheimer’s disease, Parkinson’s disease – the neurons are primarily damaged.

Different brain regions have different tasks and must be specifically expanded as required. In the forebrain of mammals, the cerebral cortex – which is responsible for cognitive function – is usually highly folded and expanded. The more folds and wrinkles there are, the larger the surface and the better the brain can absorb and process information. In humans, the brain surface of the fetus is mostly smooth until approximately the sixth month of pregnancy: it is not until after that the folding begins. Until this study, it was completely unknown which mechanisms trigger the expansion and folding of the brain in the course of fetal development. Now for the first time, Magdalena Götz and her team have identified the corresponding molecular mechanism in the mouse model: The responsible protein is the nuclear protein Trnp1, whose dynamic regulation triggers an enormous proliferation of neurons of the cerebral cortex and stimulates folding even in mice that normally exhibit smooth, unfolded brains. Trnp1 is thus a key protein for the expansion and folding of the cerebral cortex. During fetal development it is dynamically controlled: In the early phases of development Trnp1 levels are high. This favors the formation of radial glial cells, and specific brain regions expand. Later, Trnp1 levels drop again to lower levels. As a consequence, the formation of various progenitor cells and glial cells is stimulated, and a particularly large number of newly formed neurons arrange themselves in a folded structure. This molecular mechanism is particularly interesting because both the expansion and the folding of the brain are regulated by the same molecule – Trnp1. Thus, Trnp1 represents a very promising approach for investigation of the cellular and molecular mechanisms underlying these complex processes – an approach that Götz and her team want to pursue further.

Trnp1 Regulates Expansion of Cerebral Cortex

The cerebral cortex is the neuron-rich outer layer of the cerebrum. Depending on the region, it is only two to five millimeters thick and is part of the gray matter of the cerebrum. The nerve fibers of the neurons of the cerebral cortex extend below the cortex and form the white matter of the cerebrum that consists largely of myelinated nerve fibers bundled into tracts.

During the fetal development of many mammals the cerebral cortex increases in size and becomes folded. Scientists of Helmholtz Zentrum München have now succeeded in identifying the key protein responsible for this process.

The responsible protein is the nuclear protein Trnp1, whose dynamic regulation triggers an enormous proliferation of neurons of the cerebral cortex and stimulates folding even in mice that normally exhibit smooth, unfolded brains. Trnp1 is thus a key protein for the expansion and folding of the cerebral cortex. During fetal development it is dynamically controlled: In the early phases of development Trnp1 levels are high. This favors the formation of radial glial cells, and specific brain regions expand. Later, Trnp1 levels drop again to lower levels. As a consequence, the formation of various progenitor cells and glial cells is stimulated, and a particularly large number of newly formed neurons arrange themselves in a folded structure. This molecular mechanism is particularly interesting because both the expansion and the folding of the brain are regulated by the same molecule – Trnp1. Thus, Trnp1 represents a very promising approach for investigation of the cellular and molecular mechanisms underlying these complex processes – an approach that Götz and her team want to pursue further.


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2012: Federal Cross of Merit with ribbon
2009: Alzheimer Research Award of the Hans and Ilse Breuer Foundation
2007: Hansa Family Award and Gottfried Wilhelm Leibniz Prize of the German Research Foundation
2006: Habilitation
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For the first time the formation of new nerve cells from somatic cells of the human brain has succeeded: Specific cells of the adult human cerebral cortex could be reprogrammed into functioning neurons with the aid of two transcription factors.

The brain consists of two main types of cells: the neurons, which transmit information, and the glial cells, which have a supporting function and are involved in the metabolism of the brain. In many degenerative diseases of the brain – stroke, Alzheimer’s disease, Parkinson’s disease – the neurons are primarily damaged.
Roquin proteins control the activation and differentiation of T cells by regulating their gene expression at the level of messenger RNA. The function of the RNA-binding proteins is first and foremost to ensure immunological tolerance and to prevent excessive immune reactions – such as in autoimmune diseases. Katharina Vogel and Stephanie Edelmann of the Institute of Molecular Immunology showed how the two proteins, Roquin-1 and Roquin-2, can replace each other functionally and which consequences result from the combined loss of both Roquin genes. In the case that the Roquin-1 san form is present in a single point mutation, Roquin-1 inhibits the function of Roquin-2. In the absence of Roquin-1, Roquin-2 takes over and compensates for its function. The proteins are consequently interchangeable in their molecular function and fulfill a kind of reserve function for each other. The loss of both Roquin genes leads to an uncontrolled accumulation of effector T cells and particularly of follicular helper T cells. If these T cells then trigger an immune response against the body’s own structures, a clinical picture emerges that is very similar to lupus erythematosus, an autoimmune disease that attacks the skin and internal organs. A single point mutation in the Roquin-1 gene, i.e. the exchange of a single amino acid in the protein, leads to such a disease. Interestingly, in this case the Roquin-2 protein is unable to take over the function of the defective Roquin-1, resulting in a complete loss of the Roquin function. The research team also identified the molecular targets of the Roquin proteins, the Icos and Ox40 costimulator mRNAs.

This research demonstrates that the Roquin-1 and 2 proteins are of great importance for T cell differentiation in immune reactions. In future studies, the focus will be on elucidating the regulation of these factors because this regulation mechanism can be used as a therapeutic target in the treatment of autoimmune diseases.


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Personalized Leukemia Therapy Appears within Reach

Cancer is caused by mutations in the genome due to different factors. The gene mutations mostly affect the regulators of cellular metabolism or cell growth. As a consequence, the cells undergo malignant transformation and proliferate in an uncontrolled manner. Many of such gene mutations have been identified in leukemia.

In about one third of patients with acute myeloid leukemia (AML) the malignant cells have a mutation in the growth-regulating receptor FLT3. As the team of scientists headed by Dr. Philipp Greif and Professor Karsten Spiekermann have now discovered by means of exome sequencing, blood cancer cells from a substantial number of patients in a subgroup of AML (so-called core-binding factor leukemias) also carry mutations in this receptor. The gene alterations at position N676 were previously unknown and now allow a new classification of this leukemia form, which is characterized by a particularly high cell count. In addition, according to the researchers, the newly identified FLT3 receptor mutations in this leukemia group provide a new target for personalized treatment of the disease. Inhibitors of the FLT3 receptor are already available and can now be administered to the affected patients.

The study was conducted by the clinical cooperation group “Pathogenesis of Acute Myeloid Leukemia”, a joint institution of Helmholtz Zentrum München and the Department of Internal Medicine III at the University Hospital of Munich. The aim of the clinical cooperation group (CCG) is to identify leukemia-causing alterations at position N676 and to investigate why certain mutations can cause leukemia. The head of the CCG Wolfgang Hiddemann emphasizes the importance of this interdisciplinary collaboration: The results show in an exemplary way how innovative research methods, such as high-throughput DNA sequencing, allow discoveries, even in structures that have already been thoroughly examined. These insights into the molecular basis of the disease open up new treatment options for patients.

Specific mutations of the FLT3 receptor may contribute to the development of acute myeloid leukemia. The FLT3 receptor regulates cell growth; activating gene mutations promote uncontrolled proliferation of white blood cells. This finding of the clinical cooperation group “Pathogenesis of Acute Myeloid Leukemia” can be used to develop a therapy by means of specific inhibitors that inhibit the growth signal.

Acute myeloid leukemia (AML) is the most common cancer of the hematopoietic system occurring in adults. Only about 25 to 30 percent of the patients survive the first five years after diagnosis.
Further Decryption of the Epigenetic Code

Scientists of the research unit Molecular Epigenetics, in collaboration with colleagues from other institutions, have decrypted mechanisms that control the cell nucleus enzyme RNA polymerase II so that selected genetic and epigenetic information is processed. The elucidation of such processes is a basis for better understanding diseases, and for developing new therapeutic approaches.

The central function of the enzyme RNA polymerase II is the transcription of genetic information stored in the DNA into mRNA, which then transports this information from the cell nucleus to the ribosomes and there regulates protein biosynthesis. In addition, however, RNA polymerase II – as has recently been discovered – is also crucial whenever epigenetic information is stored in the cell and retrieved again. Scientists of the research unit Molecular Genetics, together with colleagues from Ludwig-Maximilians-Universität München and the Universities of Marseille and Barcelona, have explored important new details of these mechanisms.

With many slight alterations of amino acids, cells are able to store information in the chromatin of the cell, in order to transcribe this later when needed or to delete it. The RNA polymerase II is directly involved in this process with its carboxy terminal domain (CTD) – a sequence of seven amino acids repeated 52 times. As Dirk Eick and his colleagues have now found, not only are the serine amino acids reversibly modified in the CTD by means of phosphorylation, but also the amino acids threonine and tyrosine. The combinatorics of how the large number of these three amino acids is altered in the RNA polymerase II regulates important flows of information in the cell and is the central component for the regulation of gene expression in all multicellular organisms. The CTD of RNA polymerase II thus has the function of linking genetic and epigenetic information in the cell. This further decryption of epigenetic mechanisms enables a better understanding of the molecular process of cell differentiation, as well as pathological and degenerative developments in the cells. Among other research questions, the scientists want to investigate how certain environmental factors can influence the cells epigenetically.

Scientists of the research unit Molecular Epigenetics, together with colleagues from other institutions, have decrypted mechanisms that control the cell nucleus enzyme RNA polymerase II so that selected genetic and epigenetic information is processed. The elucidation of such processes is a basis for better understanding diseases, and for developing new therapeutic approaches.

The term epigenetics refers to the genomic regulation mechanisms which are not specified in the DNA sequence. Epigenetic modifications, e.g. the methylation of histone components of the chromosomes, can contribute to determining the fate of genes and to a certain extent can be passed on to subsequent generations.

RNA Polymerase II (POL II) transcribes the information of all protein-coding genes into mRNA and is a central hub for storage and retrieval of epigenetic information in the cell. The carboxy terminal domain (CTD) thus links genetic and epigenetic information.
Intellectual Disability Is Caused by Spontaneous Mutation

Severe congenital intellectual disability, which is not associated with a known disease syndrome such as Down syndrome, is caused to a high percentage by new mutations in the genome of the child and is not inherited from the parents to the child. This is the result of a study by researchers from the Institute of Human Genetics, Helmholtz Zentrum München, which they carried out together with partners from the network ‘Mental Retardation’ in the National Genome Research network (NGFN) and with researchers from the Universities of Erlangen, Essen and Zurich. To this end, the scientists studied the genomes of 51 patients who were affected by congenital intellectual disability and the genomes of their parents. Tim Strom and Thomas Meitinger of the Institute of Human Genetics carried out exome sequencing for the mutation analyses in which selectively the DNA segment was investigated that encodes proteins and other functional products. In comparison to a control group, they identified in the genomes of the patients a significantly higher number of point mutations and small insertions and deletions. In particular, the number of mutations leading to significant damage of the respective protein was increased. The mutations were found in many different genes, and only in a few genes did the researchers find new mutations in more than one person. The authors of the study conclude that a large proportion of severe congenital intellectual disability is probably caused by new mutations. With the aid of exome sequencing, intellectual disability will be able to be diagnosed much faster and more easily. The scientists assume that in the future, the method will become a standard procedure. The good news for the affected parents is that in future pregnancies there is only a slight risk of having a child with an intellectual disability.

Intellectual disability (ID) affects about two percent of the population. Although most cases have an underlying genetic cause, to date only a few genetic defects have been identified.

New Insights into the Genetic Mechanisms of Red Blood Cell Formation

Disturbances in red blood cell formation often lead to anemia. This is a common condition that can cause cognitive impairment, growth retardation, and impaired physical capacity. Scientists of the Institutes of Genetic Epidemiology, Epidemiology I, and Epidemiology II of Helmholtz Zentrum München have been instrumental in the identification of a total of 75 independent loci that play an important role in human red blood cell formation. For this purpose, a genome-wide association study (GWAS) was carried out on 135,000 individuals. For 43 of the identified 75 genes, no association with parameters of erythrocytes (red blood cells) had hitherto been detected. The identified genetic loci contribute to the variance of the properties of the erythrocytes in the general population. In collaboration with research groups from the UK and the Netherlands, the research groups led by Christian Gieger and Janina Ried of the Institute of Genetic Epidemiology, Christine Meisinger of the Institute of Epidemiology II and Angela Döring of the Institutes of Epidemiology I and II studied a total of six parameters of red blood cells, including the number and size of the erythrocytes and the hemoglobin values. Further biological analyses provided insights into biological mechanisms and signaling pathways in the formation and function of erythrocytes, which shall be studied in more detail in future research projects. These findings may then also contribute to a deeper understanding of genetic abnormalities of blood cells and congenital forms of anemia. In subsequent studies, the researchers want to identify genetic factors influencing clinically relevant abnormalities of the red blood cells.

By means of a genome-wide association study (GWAS), researchers have identified 75 gene loci that play a role in human red blood cell formation, enabling them to take a closer look at hematological abnormalities such as anemia.

Genome wide association studies (GWAS) are advanced analysis techniques used to detect genetic differences between healthy subjects and people with conditions such as anemia or diabetes. The aim is to identify associations between genetic variations and external characteristics and thus to identify genetic risk factors for the development or course of a disease.
DNA Methylation Plays Important Role in Human Metabolism

Aging processes, but also environmental and lifestyle factors such as smoking or diet cause biochemical modifications in the DNA during the course of a lifetime. This can lead to methylation of the DNA components, whereby methyl groups are added without changing the actual DNA sequence. These processes, known as epigenetic changes, can impact gene function. Scientists of the Institute of Genetic Epidemiology and the Research Unit Molecular Epidemiology carried out an epigenome-wide association study to determine if there are any associations – and if so which associations – between epigenetic processes and health consequences for the metabolism. For this purpose, the team led by Christian Gieger and Melanie Waldenberger in collaboration with Karsten Suhre from Weill Cornell Medical College in Qatar analyzed blood samples of more than 1800 participants of the KORA study (Cooperative Health Research in the Augsburg Region). In the samples they analyzed more than 457 000 positions in the DNA to detect epigenetic alterations and compared these with concentrations of 649 different metabolites. The analysis showed that methylation of 28 DNA segments changed a number of important metabolic processes.

In the respective DNA regions, already known disease-associated genes were also found, such as the gene TXNIP, which regulates glucose metabolism and is associated with the development of diabetes mellitus. Consistent with this finding, altered concentrations of metabolites of the lipid and glucose metabolism were found in the methylated TXNIP. Moreover, genes that can be biochemically altered by smoking affect different metabolic activities.

The study provides new insights into how lifestyle factors can influence the metabolism through DNA alterations. The results will be used to develop new diagnostic and therapeutic approaches for lifestyle-related diseases.

Biological functions of organisms are also controlled by higher-level regulatory mechanisms, which are grouped under the term epigenetics. Epigenetic modifications, such as methylation of protein components of chromosomes, can help to determine the fate of genes and are passed on to some extent even to subsequent generations.
Detecting the Identities of “Unknown Metabolites”

A combined analysis of genetic variants and actual metabolic changes shows relationships between risk factors and the development of common diseases and thus provides evidence of standardized measurable biomarkers. Thus far, however, only such metabolites could be considered that the measuring devices recognize. The research team led by Jan Krumsieck and Gabi Kastenmüller of the Institute of Bioinformatics and Systems Biology and the Institute of Computational Biology has developed a method to also identify unknown metabolites. The application of the method on risk factors that have not been chemically characterized until now allows conclusions to be drawn about which processes influence the development of a disease, but also about the individual’s response to drug therapies. On the basis of data from the KORA population study (Cooperative Health Research in the Augsburg Region), the scientists detected in the blood the biochemical identity of nine previously unknown metabolites and associated 97 compounds to specific metabolic pathways, including risk factors for high blood pressure and insulin resistance. A new marker for impaired liver detoxification may in the future be a chemical derivative of vitamin C whose concentration is also genetically influenced. This blood value can indicate to the physician how effectively the liver detoxifies a patient’s body and thus aid in the selection of a suitable drug for this particular patient. Personalized therapies that are based on a combination of genetic and biochemical risk factors can offer chances of an improvement the quality of life of a cure of common diseases, such as type 2 diabetes, which is currently incurable.

Scientists at the Institute of Bioinformatics and Systems Biology have developed a method to identify previously unknown metabolites in the blood that may be associated with genetic variations. This could be a further boost for the development of personalized therapies.

Metabolomics is the study of the characteristic metabolic traits of an organism that are present in the metabolites of a blood sample. The analysis is performed via mass spectrometry or magnetic resonance imaging.

Imaging Modalities – two better than one

Scientists of the Institute of Biological and Medical Imaging and the Institute of Experimental Genetics led by Vasilis Ntz zachristos have achieved a milestone in imaging diagnostics: By combining two established, non-invasive imaging techniques – X-ray computed tomography (XCT) and a camera-based hybrid fluorescence molecular tomography (FMT) system – they succeeded for the first time in obtaining a 360-degree view from the inside of a living organism. With the combined XCT-FMT method, which combines the advantages of the two proven imaging techniques, internal structures and organs can be examined in detail in the living organism. For example, it is possible – due to the 360-degree view – to exactly localize pathologically altered tissue in vivo. Through the combination of the two methods, significantly better results can be achieved than with a stand-alone method. In living mice the scientists were able to observe bone growth, obtain images of subcutaneous tumors in the neck area in high resolution and to diagnose lung cancer. The new combination of the two methods enables more precise diagnosis as to where the tissue is pathologically changed than when the techniques are used individually. In further steps, the scientists want to refine this in-vivo method so that it can be used in pre-clinical diagnosis in patients – for example in the early detection of tumors. The Institute of Biological and Medical Imaging explores in vivo imaging technologies for the life sciences. It develops systems, theories and methods for imaging and image reconstruction as well as animal models for the testing of new technologies on the biological, pre-clinical and clinical level. The aim is to provide innovative tools for the bio-medical laboratory, for diagnostics and for the monitoring of therapies for human diseases.

In X-ray based computed tomography, different images taken with the aid of x-ray are assembled in the computer to provide three-dimensional visualization of the investigated structures. In fluorescence tomography the distribution of a fluorescent substance which was administered prior to the test is shown three-dimensionally and non-invasively in the tissue and organs.
Lifestyle Factors Affect Metabolite Profile

Cigarette smoking causes a multitude of changes in metabolite concentration, which increase the risk of multiple diseases. When an individual quits smoking, smoking-related changes in human serum metabolites are reversible. These results are consistent with previous findings that the risk for cardiovascular disease — such as a myocardial infarction — reduces after smoking cessation. Scientists of the Research Unit Molecular Epidemiology, of the Institute of Epidemiology II and of the Institute of Experimental Genetics analyzed blood samples from more than 1,200 participants of the population-based Cooperative Health Research in the Region of Augsburg (KORA) cohort. Blood samples and smoking status of these individuals were collected at two time points: a baseline survey conducted between 1999 and 2001 and a follow-up after seven years. Overall, through the analysis of the metabolite profiles, the team led by Rui Wang-Sattler, Tao Xu, Jerzy Adamski and Annette Peters identified 21 smoking-related metabolites, which are enriched in amino acid and lipid pathways. 19 out of the 21 metabolites were found to be reversible in former smokers, including arginine, glutamate and lyosphosphatidylcholines, which have been previously reported to be associated with the risk reduction of cardiovascular diseases. These results indicate the remarkable benefits of smoking cessation and provide a link to cardiovascular disease benefits. The identified smoking-related metabolites pinpointed disturbed pathways, which are useful to elucidate further health consequences of nicotine consumption. The study therefore represents a meaningful metabolomics approach with which the molecular signatures of lifestyle-related environmental exposures and diseases can be studied.

Smoking-related changes in human serum metabolites are reversible after smoking cessation, consistent with the known cardiovascular risk reduction and other health consequences.

The Cooperative Health Research in the Region of Augsburg (KORA) has been studying the health of thousands of people from the Augsburg area for almost 30 years. The aim is to understand the effects of environmental factors, behavior and genes. The core topics of the KORA studies are questions about the development and course of chronic diseases, in particular heart attack and diabetes mellitus. To this end, research is conducted on risk factors from health behavior, the environment and genetics.
Bioinformatics for Stem Cell Research

Scientists of the Institute of Computational Biology at Helmholtz Zentrum München, together with colleagues from the Stem Cell Institute and the Institute for Medical Research of the University of Cambridge, have identified important differentiation pathways of stem cells. The Munich scientists were responsible for the characterization of transcriptional networks in blood stem and progenitor cells using high-throughput single-cell gene expression analysis.

Out of a pool of nearly 600 single primary blood stem and progenitor cells isolated from mouse bone marrow, 18 transcription factors were identified which can cause a further differentiation of the progenitor stem cells. Transcription factors are responsible for turning gene expression "on" or "off". By means of a statistical mapping technique known as dimensionality reduction, Florian Büttner and Fabian Theis identified specific patterns in the pairings of these transcription factors. The pairings could be correlated positively or negatively with characteristic stages of cell maturation and therefore provided clues about the functions of the individual transcription factors and the cell fate. Within the expression patterns, the scientists also found previously unrecognized relationships between the factors Gata2, Gfi1 and Gfi1b. This is of particular importance because especially for Gata2 and Gfi1, recently a correlation has been described with leukemia: Gata2 is thought to promote the formation of malignant cell clones, whereas Gfi1 plays a more protective role.

The reconstruction of individual transcription factor profiles and the identification of their networks offer the opportunity not only to understand the physiological differentiation and development of cells, but to better understand degenerative and malignant processes.

In collaboration with the University of Cambridge, scientists of the Institute of Computational Biology have identified important differentiation pathways of stem cells by means of expression patterns of these transcription factors. The pairings could be correlated positively or negatively with characteristic stages of cell maturation and therefore provided clues about the functions of the individual transcription factors and the cell fate. Within the expression patterns, the scientists also found previously unrecognized relationships between the factors Gata2, Gfi1 and Gfi1b. This is of particular importance because especially for Gata2 and Gfi1, recently a correlation has been described with leukemia: Gata2 is thought to promote the formation of malignant cell clones, whereas Gfi1 plays a more protective role.

The reconstruction of individual transcription factor profiles and the identification of their networks offer the opportunity not only to understand the physiological differentiation and development of cells, but to better understand degenerative and malignant processes.

Cell differentiation is regulated by a complex interaction of external influences on the internal cell environment, in which so-called transcription factor-regulated-networks are of particular importance. Transcription factors are responsible for activating or repressing gene expression.


Network of 18 transcription factors involved in the differentiation of bone marrow stem cells into various blood and immune cells

Functional relationships

Direct protein-protein interactions
Mapping of the Barley and Bread Wheat Genomes

In the framework of the International Barley Sequencing Consortium, scientists at the Helmholtz Zentrum München have made a major contribution to deciphering and analyzing the barley genome and to develop new approaches for molecular breeding. The research of the International Barley Sequencing Consortium, which along with other partners, includes scientists led by Klaus Mayer at the Department of Plant Genome and Systems Biology, provides a detailed view into the barley genome. For the first time a high-resolution genome overview was created for a genome that by far exceeds the size of the human genome. In addition, the team was able to gain insight into gene regulation and make comparisons between wild barley and cultivated strains. Thus, an in-depth molecular understanding of the inventory of cereal genomes and a first glimpse into molecular circuits was obtained.

Together with international partners, a team of the Department of Plant Genome and Systems Biology has created ordered sequence resources of the highly complex genomes of barley and bread wheat. Both crops are of enormous importance.

Barley is one of the earliest domesticated and most important cereal crops. The barley genome is diploid, contains slightly more than 26 000 genes and includes 5.1 billion base pairs (5.1 Gb). The bread wheat genome, with 17 billion base pairs (17 Gb), is not only much larger but also contains considerably more genes – approximately 96 000. A wheat cell is hexaploid and has six copies of its chromosomes.

The findings are seen as an important basis to accelerate the breeding of barley varieties that e.g. show improved resistance or are better adapted to climate change. At the same time, the barley genome served the researchers as model for the more complex bread wheat genome. Here the team headed by Klaus Mayer, together with British scientists from the Universities of Bristol und Liverpool and the John Innes Centre carried out and published a first genome analysis. Along with rice and corn, wheat is the most important cereal crop. The bread wheat genome is hexaploid (contains six copies) and contains approximately 96 000 genes. Due to its size and complexity, it has not yet been fully sequenced. The now published genome atlas is an important step towards understanding the interplay of the different genome copies of this cereal and to enable molecular breeding even for wheat.

Casting Light on the Evolution of Nightshades

The Tomato Genome Consortium (TGC), a group of more than 300 scientists from 14 countries, has sequenced the genome of the domesticated tomato and its closest wild relative (Solanum pimpinellifolium). Together with other research centers in Germany, Helmholtz Zentrum München was involved in the bioinformatics analysis and annotation of the genome sequences. The research group led by Klaus Mayer at the Department of Plant Genome and Systems Biology was responsible for data management, database infrastructure and dissemination as well as gene family and comparative genome analyses. The sequences provide the most detailed insights to date into the tomato genome. Thus, the approximately 30 000 genes of the tomato with their genomic position and a large portion of their likely functions are now known. The tomato is a member of the Solanaceae or nightshade family. The Solanaceae family includes potatoes, bell peppers and eggplant. Worldwide, it is the most important family of vegetable plants – both with regard to its economic significance and the quantity produced. Members of the Solanaceae family are used as food, spices and as medicinal plants. The new sequences provide a reference to identify important genes in related species. The sequences also open up insights into the diversification of the tomato and the adaptation to new environmental conditions. They reveal that 60 million years ago triplication of the tomato genome occurred. After that, a large part of the triplicated genes were lost. However, some exist even until today and control the most important breeding traits of the tomato including strength, fleshiness and fruit coloring. The results are an important basis for further research to optimize the production of tomatoes and other crops. The resistance to pests, diseases and drought, which in part have been lost during the domestication of the plant, is of particular importance.

In gene sequence annotation, the position of exons and introns, protein-encoding regions including the encoded protein and its possible functions, promoter elements and repetitive DNA elements is attached (annotated) to the actual DNA sequence.

With the participation of Helmholtz Zentrum München, the Tomato Genome Consortium, a group of more than 300 scientists from 14 countries, has sequenced the tomato genome with its approximately 35 000 genes. The Department of Plant Genome and Systems Biology manages a range of several plant genome databases, provided important infrastructure for the data management and carried out gene family and comparative genome analyses.

Original Publication:


Further authors from Helmholtz Zentrum München: Thomas Nussbaumer, Heidrun Gundlach, Mihaela Martinez, Manuel Spannagl, Matthias Pfeifer – Department Plant Genome and Systems Biology

Original Publication:

Further authors from Helmholtz Zentrum München: Manuel Spannagl, Heidrun Gundlach, Remy Bruggmann – Institute of Bioinformatics and Systems Biology/Munich Information Center for Protein Sequences (MIPS)
How Roots Branch Out

Plants initiate lateral root formation deep within the primary root. For lateral roots to reach the soil, they first must break through the rigid, overlying tissue layers of the primary root. To initiate lateral root emergence, the plant hormone auxin is required. This also stimulates processes to weaken the cell walls. In the current study, it was found that the increased auxin concentration also causes aquaporin expression to change in the cell membranes of the new organ and the surrounding tissue. Aquaporins facilitate water movement across the cell membranes of plant cells. This regulation is also critical for how rapidly the newly initiated lateral roots can penetrate the tissue. The researchers led by Anton Schäffner at the Institute of Biochemical Plant Pathology have conducted research on this topic together with colleagues from the Centre for Integrative Plant Biology of the University of Nottingham in the UK, the Institut Nationale de la Recherche Agronomique in Montpellier, France, and the Universidad de Extremadura, Badajoz, Spain. Researchers at Helmholtz Zentrum München investigated in particular the phenotypes of plants whose aquaporin expression had been genetically modified and determined the temporal and spatial expression patterns of aquaporins in the emerging lateral root. The colleagues in France contributed essential physiological data. Mathematical modeling based on the experimentally found expression patterns was also crucial; it enabled the British partners to correctly predict the phenotypic findings. The consortium’s insights gained on the model plant Arabidopsis thaliana (thale cress), may be useful for plant breeding: Through the formation of lateral roots, plants not only have a better grip in the soil but can also absorb more water and minerals. This is a great advantage for plant growth – especially with reduced water availability in soils due to climate change.

The expression of aquaporins is locally regulated by the increased auxin levels that initiate lateral root formation. These changes significantly affect the rate of lateral root emergence.

Aquaporins are proteins in the cell membrane of organisms that regulate water permeability. Thus, they also influence the rate of pressure changes within plant cells driving their expansion growth.
Helmholtz Zentrum München turns promising scientific approaches from basic research into innovations. It ensures that all innovative know-how is being produced at the Center is protected by patents and out-licensed for commercialization. Insights from basic research are further developed and applied in spin-offs and in collaborations with competent industrial partners.

In 2012 and 2013, four new companies were launched as spin-offs from Helmholtz Zentrum München. Thus, the Center translates excellent science into specific applications and creates new impetus in the field of data management, clinical imaging, immunotherapy and radiation dosimetry.

Clueda AG, founded in 2012, is a software company that brings intelligent prediction, analysis and decision support tools to market maturity for different industries. In 2013 the company received the Best in Big Data Award of the weekly magazine Computerwoche for an analysis system it developed together with a German investment bank.

The start-up company SurgVision B.V., launched in 2012, develops systems that enable molecular live imaging during surgical procedures. A first clinical study on image-guided surgical procedures for breast cancer patients is nearing completion, additional indications are being evaluated.

SurgVision developed from a collaborative project between the Institute of Biological and Medical Imaging and the University Medical Center Groningen, the Netherlands. Trianta Immunotherapies GmbH was founded in 2013 as a spin-off of the Institute of Molecular Immunology and develops immunotherapies for the treatment of cancer. For its spin-off project, the team led by Institute Director Prof. Dr. Dolores Schendel received an m² award of the Bavarian Ministry of Economic Affairs endowed with 500,000 euros.

Dosimetrics GmbH was also founded in 2013. The company is a manufacturer and service provider of personal dose monitoring systems for ionizing radiation. Based on the research of the personal dosimetry service at Helmholtz Zentrum München, the largest personal dosimetry service in Europe, Dosimetrics provides technologies for easy detection and the rapid readouts of individual doses.

With the new start-up companies, Helmholtz Zentrum München has continued its successful series of spin-offs. Since 1997, 18 spin-off companies from the Center have been founded: 15 of these are currently active on the market and employ approximately 400 people.

In the field of drug development, Helmholtz Zentrum München specifically promotes projects that are in the early phase of the value added chain. The portfolio currently comprises developmental projects from the areas of diabetes, neurodegeneration, autoimmune diseases and cancer. The major aim is the identification and development of innovative drugs. Five of the 27 newly registered patents in 2012 and 2013 refer to new compounds. The entire patent portfolio of the Center currently covers 150 patent families.

To identify new target structures for drugs against diabetes, a strategic research collaboration was launched in 2013 between the Institute for Diabetes and Obesity and Sanofi Aventis Deutschland GmbH. The research collaboration is initially designed to last for three years.

Translational Research
Translational research, which aims at the benefit for patients, is an essential element of the scientific strategy at the Center. The objective is to enable the reliable stratification of patient groups and to develop preventive and treatment approaches tailored to the individual patient. Key success factors are the close connection between excellent basic research, continuous advancements in platform technologies and differentiated model systems with large population cohorts, and clearly defined patient populations.

The Center implements this principle in three translational centers, eleven clinical cooperation groups and a translational project portfolio in collaboration with clinical partners.

Translational Centers
There are three regional translational centers in the fields of lung, diabetes and allergy research that closely combine basic research, technology platforms and clinical research in a long-term perspective. While both the Diabetes Study Center and the Munich Allergy Research Center collaborate with Technische Universität München, translational research in cooperation with Ludwig-Maximilians-Universität München and the Asklepios Fachkliniken München-Gauting has been implemented at the Comprehensive Pneumology Center since 2013, following the successful appointment of the Chair of Clinical Pneumology at the University Hospital.

Clinical Cooperation Groups
In eleven clinical cooperation groups, defined clinical-scientific hypotheses are elucidated with the aim of achieving clinical proof of concept. Four of them develop personalized cellular therapy approaches for clinical application. A phase I/II trial for treatment of CMV infection after bone marrow transplantation by adoptive T-cell transfer was recently completed and is being evaluated. Further projects in or shortly prior to clinical trials include cell vaccination in acute myeloid leukemia, NK-cell transfer in non-small cell lung cancer and prophylactic CMV and EBV-specific T-cell transfer after stem cell transplantation.

Since 2013, two clinical cooperation groups have been participating in observational studies of the German Center for Diabetes Research (DZD). For the Prediabetes Lifestyle Intervention Study PLUS, these groups investigate whether lifestyle changes with respect to diet and physical activity positively influence the risk for the development of type 2 diabetes. Within the German Diabetes Study DDS, a differentiated long-term observation of newly diagnosed diabetes patients is being carried out.

In cooperation with the Department of Radiation Oncology, Ludwig-Maximilians-Universität München, the clinical cooperation group “Personalized Radiotherapy in Head and Neck Cancer” was established in 2013. It analyzes molecular markers for predicting the efficacy of radiotherapy for tumors of the head and neck area.

Translational Project Portfolio
To specifically strengthen the development of personalized preventive, diagnostic and therapeutic concepts, translational and have been funded since 2012. A total of nine peer-reviewed projects were supported by 2013.

Cross-Program Initiative Personalized Medicine
In the newly established Helmholtz Initiative Personalized Medicine (iMed), the Center has teamed up with four Helmholtz Health Research Centers to establish a research-driven and molecular systems medicine program which spans various indications. The initiative provides high-throughput and IT platforms for collaborative projects. The indications are cancer, metabolic and cardiovascular diseases, diseases of the nervous system as well as lung diseases and infectious diseases.
Innovation and Translation

Here we present two promising new approaches for prevention and therapy.

Spin-Offs from the Center since 1997
Antipsychotic Drugs Tested against Malignant Lymphomas

For Daniel Krappmann, in retrospect everything seems so clear and obvious. In view of their groundbreaking findings, the excitement was palpable among Krappmann and his 15-member team until the study was published: The researchers discovered that a MALT1 protease enzyme can be used to treat malignant lymphomas. The substances inhibit the enzyme MALT1, leading to the death of cancer cells. This could mean a breakthrough in cancer research.

Many years of intensive preparatory work, coupled with determination and the necessary bit of luck led to this success. Since 2008, Daniel Krappmann, head of the research unit Cellular Signal Integration at the Institute of Molecular Toxicology and Pharmacology at Helmholtz Zentrum München, has been investigating the MALT1 protease, which he had recognized as a particularly interesting enzyme. “It is the only enzyme in this class in humans, and is thus very exclusive,” the 45-year-old biologist said. He not only analyzed its enzymatic effectiveness, but using genetic methods, also explored the effects of the MALT1 protease on the immune system. In addition, his team, together with scientists from Technische Universität München, was able to show that aggressive lymphoma cells are not viable without the activity of MALT1.

After all this was known, Krappmann decided to look for compounds that can inhibit MALT1, since such substances would provide good starting points for drugs for the treatment of lymphomas or autoimmune diseases. His doctoral candidate Daniel Nagel took on the task and tested 18,000 substances in cooperation with the Leibniz-Institut für Molekulare Pharmakologie in Berlin. After many test runs and further analyses in cooperation with Charité Universitätsmedizin Berlin, it became apparent that the long-known antipsychotic drugs mepazine and thioridazine were among the best MALT1 inhibitors.

“It is a huge advantage that both drugs have long been in clinical use,” said Krappmann. “Many side effects have been extensively studied, and this allows us to quickly initiate clinical trials.” These will now begin parallel to further trials that will be carried out on the effect of the substances in autoimmune diseases.

According to Krappmann, Helmholtz Zentrum München offers excellent conditions for such research. Here researchers find expertise in a variety of disciplines, from biochemistry and immune research to preclinical testing. Meanwhile, a separate screening unit has been established for drug discovery at the Center.

Added to this was the financial support from the Helmholtz Validation Grant, the new funding instrument of the Helmholtz Association. The funding for the project amounted to around 900,000 euros, half of which came from the Helmholtz Association and the other half from Helmholtz Zentrum München. The financial support from this fund will enable scientists from Helmholtz centers to develop their project ideas into commercial results within two years. That is exactly what happened in Krappmann’s project.

The successful identification of a MALT1 inhibitor will also raise the awareness of the pharmaceutical industry for developments and projects within the Helmholtz Association and, over the medium term, significantly promote strategic partnerships. Thus, innovative solutions for patients and even personalized medicine approaches will become possible: “In the future, special biomarkers may enable the identification of patients who respond to treatment with a MALT1 inhibitor,” said Daniel Krappmann. “Our long-term goal is quite clear – to replace standard treatment with personalized treatment, i.e. with a treatment protocol designed for the individual patient.”

All in all, a great success for Innovation Management at Helmholtz Zentrum München. Here in an exemplary way, basic research findings are translated into applications – thus increasing the value creation of the Center immensely. “It is only possible to pursue such research approaches consistently in an interdisciplinary research environment,” Krappmann said. “With our study we have shown that it really can be done!”

Daniel Krappmann is studying the MALT1 protease enzyme as new approach for the treatment of malignant lymphomas. With support from the Helmholtz Validation Grant and the Department of Innovation Management, the team of the research unit Cellular Signal Integration led by Krappmann found potential research inhibitors, which then were licensed for therapeutic further development. Image: signaling protein visualized with an immunofluorescence microscope.

Publications:


BRIEF PROFILE

PROF. DR. DANIEL KRAPPMANN

Head of the research unit Cellular Signal Integration and deputy director of the Institute of Molecular Toxicology, Helmholtz Zentrum München since 2004:
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2002-2005:
Junior research group leader, Max Delbrück Center, Berlin
1997-2002:
Postdoc, Max Delbrück Center, Berlin

Daniel Krappmann has been investigating the MALT1 protease as a new approach for the treatment of malignant lymphomas. With support from the Helmholtz Validation Grant and the Department of Innovation Management, the team of the research unit Cellular Signal Integration led by Krappmann found potential research inhibitors, which then were licensed for therapeutic further development. Image: signaling protein visualized with an immunofluorescence microscope.
Spearhead of Diabetes Prevention

The incidence of a disease is rising, and no one knows why: For years doctors have observed that the number of cases of type 1 diabetes in children – especially young children – and adolescents is rising throughout the world. In Germany, the rate of new cases is currently increasing by three to five percent annually. The causes for this increase are still unknown: possible culprits may be environmental factors that have an effect in the womb or in early childhood, for example early nutrition, viral infections or changes in the immune system through improved hygiene, but also the development of the microbiome of the digestive system in early childhood and the bacterial colonization of the intestine.

At the Institute of Diabetes Research at Helmholtz Zentrum München, scientists under the direction of Anette-Gabriele Ziegler are seeking to find the causes of type 1 diabetes, to elucidate the disease course and to combat the disease. Type 1 diabetes – in contrast to the much more frequent type 2 diabetes – is triggered by an autoimmune process. As a result of genetic alterations or environmental influences, the insulin-producing cells – the beta cells in the pancreas – are destroyed. Often children and adolescents are affected. When approximately 80 percent of these cells have failed, there is a dramatic rise in blood glucose levels leading to the outbreak of the disease. Without insulin treatment, the outcome of the disease would be fatal.

The physician Ruth Chmiel and the biologist Florian Haupt are working at the Institute of Diabetes Research to develop a vaccine against the dangerous disease. “By detecting certain antibodies in the blood we can diagnose the dysregulation of the immune system, which ultimately leads to the outbreak of the disease, at an early stage,” said Ruth Chmiel. “Practically all individuals in whom two or more of these antibodies have been detected develop type 1 diabetes within 15 to 20 years after diagnosis. If detected early, there is still time for preventive immunotherapy.”

Within the framework of the Intranasal Insulin Trial (INIT II) and the Oral Insulin Trial, the two scientists select appropriate German candidates who can participate in the trial of such a vaccine. Whoever has close relatives with type 1 diabetes and in whose blood the characteristic autoantibodies can be detected can take part in the trial. The subjects take one capsule with insulin daily or are treated with intranasal insulin spray once a week. “The immune system of the body can thus gradually get used to the insulin,” explained Chmiel. “It acts directly on the nasal mucosa and in this way does not disturb the metabolism.”

First successes of the vaccine have already been confirmed: Evaluations of a trial in the U.S. have shown that through the oral administration of insulin in young children and in individuals with high autoantibody titers, the onset of diabetes can be delayed significantly.

The trials in Munich will be accompanied by projects that address fundamental questions. “In translational projects at Helmholtz Zentrum München, we are studying how changes in the metabolism affect the development of type 1 diabetes,” said Florian Haupt. “In addition, cells of the immune system are being analyzed to elucidate the underlying disease processes.” Helmholtz Zentrum München is now right at the interface of basic research and the translation of the findings into medical practice. The Institute of Diabetes Research is, so-to-speak, the spearhead of diabetes research in Germany.
The focus of Human Resources Development at Helmholtz Zentrum München is on the promotion of young scientists and high potentials, especially in the areas of professional, methodological, social and leadership skills. It is complemented by a wide range of continuing education and training courses. Both levels take into account the increasing complexity of today’s research, which takes place in an international environment in cross-linked infrastructures.

In 2012 and 2013, human resources development activities at the Center increased dynamically due to the consistent orientation towards needs and demand. More than 150 internal training events are held per year. Besides scientific topics, language and computer courses and training in management and social skills are predominant.

Furthermore, in the past two years, more than 70 moderated team workshops were held under supervision of Human Resources Development. The workshops mainly focused on leadership and cooperation topics as well as changes in processes, structures, roles and responsibilities. The team approach was also applied to specific training topics that have to be implemented in and adjusted to particular organizational units, such as project and time management or systematic personnel selection. Individual training courses and support for managers and potential executives were also expanded. In this context the implementation of an internal developmental program for managers and management trainees plays an important role.

Based on individual advisory consultations, external training programs are also offered and arranged. For the qualification of science managers and administrators the training program of the Center for Science Management (ZWM) in Speyer and the Helmholtz Management Academy are especially suitable.

Coaching and differentiated mentoring programs supplement the portfolio of effective development measures. These include – in addition to the individual support provided by Human Resources Development – offers of the Helmholtz Association such as the mentoring program for young women in science, the shadowing program for employees in the administrative-technical area and a cross-company mentoring program in the Munich region.

Talent Management

Talented scientists and outstanding staff are elemental to the success of Helmholtz Zentrum München. Excellent researchers and competent staff in science management and in the administration and technical infrastructure require a strategic human resources management. This includes human resources development which is systematically oriented on the needs of various target groups and on the Center’s strategy.
Continuing Education and Training

As examples, we present two participants in the “Munich Leadership Development in Science” program, which Helmholtz Zentrum München helped to initiate.
Recruiting and Promoting Talent in Science Administration

Science is not created in a vacuum, quite the contrary: Funds have to be acquired and managed; laboratories must be operated and services organized; scientists and specialists in various fields have to be recruited and hired. Only if the framework conditions are suitable, can researchers utilize their capabilities in an optimal way. That is why efficient management is needed. “In a research center such as ours, the administration must navigate between world-class science with high dynamics on the one hand and the relatively rigid requirements of the public service sector on the other,” said Uwe Bott, who heads Human Resources Development at Helmholtz Zentrum München. Both sides have to be taken into account: the researchers who want to remain as flexible as possible and who want to avoid spending too much time on administrative tasks, and the administrators who often must comply with rigid official structures and who are not particularly well paid.

However, to be successful in international competition, new processes and structures must be developed, and there is a special need for science managers who are keen in solving very specific problems in this area. “At Helmholtz Zentrum München we have established a number of options in which employees can take part in continuing education and training courses and develop further in this area,” said Bott. “We offer around 150 Center-internal training events, which in part are intensive courses on management topics such as scientific project management. There are also seminars and workshops in which employees acquire specific knowledge and skills and practice the transfer of learning objectives into daily work. Our center also participates in the Helmholtz Management Academy, whose purpose is to promote understanding between science and the administration. In addition, we have intensified our cooperation with the Center for Science Management (ZWM) Speyer; since October, five of our employees have been participating in the one-year program ‘Munich Leadership Development in Science’. It is aimed at academic and administrative leaders from universities and research institutions in the Munich region, who already have or will soon have budget and staff responsibility.”

One of the participants of the course, Barbara Ferwagner, has been working since March in the Department of Operations & Support. In her previous positions at Helmholtz Zentrum München she was able to gain experience in a number of different areas. “In order to qualify for leadership roles, it is necessary to step out once from the microcosm of one’s own center and to discuss similar issues with colleagues from other academic institutions,” she said. “There are so many different cultures and ways of organizing science administration. This exchange with other colleagues represents a great added value of the program.” In principle, the challenges are always the same: leading people, managing resources, developing strategies, communicating and implementing, balancing interests, organizing majorities, making and carrying out decisions. The day-to-day work requires from leaders a wide range of management skills and the ability to relate these to the special characteristics of science management. The ZWM program therefore offers modules on leadership and self-leadership, project management, budgeting, and employee motivation, among other topics. Barbara Ferwagner finds the concept of the course convincing, since the basic principles of a variety of skills are taught. In addition to the qualification in management responsibilities, her colleague Theresa Schmitt, who has been working as project coordinator since 2011 in the Department of Operations and Support, sees a significant added value of the ZWM program in building networks at the science location Munich. Her supervisor recommended her for the program and – just as for Barbara Ferwagner – Helmholtz Zentrum München assumes the costs; the participants themselves must devote the necessary time by means of holidays or flextime.

The thirty-two-year-old business graduate with rigourous requirements of the public service sector on the other,“...” The thirty-two-year-old business graduate with“...”
More than three fourths of the employees are science staff. The proportion of women in leadership positions is 51 percent at the research group and junior research group level.
Staff

Helmholtz Zentrum München is an attractive employer for a broad spectrum of science-oriented professions. The Center’s dynamic development and its international work environment make it an interesting place to work both for renowned researchers and for novice scientists and administrators.

In 2012, Helmholtz Zentrum München employed a total of 2148 people from 65 different countries. In 2013 the number of employees increased to 2234; the percentage of employees financed via third-party funding dropped from 29 percent to 25 percent. Over three quarters of the staff work in the scientific area; in 2012 these included 330 doctoral students, 186 postdocs and 503 scientists. In 2013 the scientific staff was made up of 528 doctoral students, 200 postdocs and 535 scientists. Research activities focus on the areas of biology, biochemistry, physics and medicine.

Equal Opportunities
Helmholtz Zentrum München views equal opportunities for men and women to be an integral part of its corporate culture. It promotes the careers of women employees and creates equal framework conditions for professional success. To improve the compatibility of work and family both for men and women in equal measure, child care options for employees’ children on the research campus are continually being expanded. In 2012 and 2013 women made up 59 percent of the workforce. The overall proportion of women in leadership positions is 34 percent; 51 percent of the research groups and junior research groups are headed by women.

Vocational Training
In addition to the promotion of young scientists, Helmholtz Zentrum München is engaged in vocational training and offers a broad spectrum of vocational training disciplines. At the end of 2012 there were 63 vocational trainees; at the end of 2013 there were 63 trainees in commercial and technical vocations as well as future animal keepers.

Women in Leadership Positions

- Percentage of women in leadership positions: 34%
- Percentage of women as leaders of research groups or junior research groups: 51%

Distribution of staff by area of work

- Science: 76%
- Infrastructure: 13%
- Administration: 11%
In 2012, the overall budget of Helmholtz Zentrum München amounted to approximately 211 million euros, with 165 million euros coming from institutional funding provided by the Federal Government and the Free State of Bavaria at a ratio of 90:10. External funds from national and international research grants amounted to 45.9 million euros, including the funds that were forwarded to third parties.
In 2013, the overall budget of Helmholtz Zentrum München amounted to approximately 224 million euros, with 172 million euros coming from institutional funding provided by the Federal Government and the Free State of Bavaria at a ratio of 90:10. External funds from national and international research grants amounted to 51.7 million euros, including the funds that were forwarded to third parties.
Project Funding and Research Cooperations

Helmholtz Zentrum München successfully takes part in in calls for proposals by the Federal Ministry of Education and Research, the European Research Framework Programme, the German Research Foundation (DFG), the Helmholtz Association of German Research Centres and other public and private organizations. In 2012 the acquired third-party funding amounted to 39.2 million euros, and in 2013 the amount was 39.1 million euros.

In public funding for Helmholtz Zentrum München, the Federal Government ranks first with approximately 12 million euros per year, followed by the European Union with almost 9 million euros and the German Research Foundation (DFG) with more than 4 million euros. At the end of 2013 there were more than 350 third-party agreements for research funding. By the end of 2013, Helmholtz Zentrum München contributed to almost 430 proposals in the 7th Research Framework Programme of the European Union. This resulted in 113 projects with approximately 63 million euros in funds from the EU for the Center.

Helmholtz Zentrum München was particularly successful in acquiring grants from the European Research Council (ERC). The Center has a total of 12 ERC grantees with a funding volume of 15.9 million euros and thus assumes a leading position among the Helmholtz Centres. Researchers at the Center who apply for grants receive intensive coaching and support from staff members of the Department of Program Planning and Management.

While the average success rate for Starting Grants and Consolidator Grants is 13.9 percent in the EU, Helmholtz Zentrum München received nine grants for a total of 34 proposals – a success rate of 26.5 percent.

In 2013 Dr. Martin Elsner and Dr. Tillmann Luders each received an ERC Consolidator Grant. The two research group leaders at the Institute of Groundwater Ecology are to receive a total of 3.85 million euros funded by the European Research Council for their research.

Prof. Dr. Magdalena Götz, director of the Institute of Stem Cell Research and Chair of Physiological Genomics at Ludwig-Maximilians-Universität, received an ERC Advanced Grant endowed with 2.38 million euros for her research on molecular mechanisms regulating neurogenesis. The grant for Magdalena Götz is one of the few Advanced Grants awarded to German women researchers in 2013: From 2400 submitted project proposals, 37 male and only 4 female Principal Investigators from Germany were awarded a grant.

Scientists at Helmholtz Zentrum München were extraordinarily successful in the last call for proposals on the topic of Health within the 7th Research Framework Programme. From nine proposals submitted by the Center in the second phase, six projects were approved with a total funding volume of more than 3 million euros.

For his contributions to German-French cooperation in the field of pneumology, Oliver Eickelberg was awarded the Gay Lussac-Humboldt Research Award 2013. Under his leadership, the Helmholtz-INSEE-M-Alliance for the Cure of Chronic Lung Disease was founded, which evolved from an initiative of the research ministries of both countries.

In 2013 the Federal Ministry of Education and Research (BMBF) supported 200 projects with 479 million euros, of which 212 projects were initiated at Helmholtz Zentrum München. The Center was thus able to solicit considerable research funds in 2012 and 2013. Particularly noteworthy are the German Plant Phenotyping Network (DPPN) with 6.1 million euros in funding and two competence networks on radiation research coordinated by the Center, together amounting to 2.1 million euros.

The BMBF research network on photonics “Ultraviolet detection and manipulation of cells and/or tissues and their molecular components” is coordinated by Helmholtz Zentrum München. From the BMBF funding initiative “e:Med – Measures to Establish Systems Medicine” the Center receives 2.0 million euros for its research contributions on heart attack, stomach cancer, neurodegeneration and alcohol addiction. Within the framework of the 2nd funding phase of the BMBF Competence Networks on Obesity and Diabetes, the Center receives a total of 0.6 million euros in funds. The German Center for Infectious Disease Research (DZIF) forwards 2.7 million euros in funding to Helmholtz Zentrum München for its research projects.

Significant projects supported by research foundations include the Max Eder Junior Research Group “Therapeutic Inhibition of Autoimmune Signals in Breast Cancer Stem Cells” led by Dr. Christina Scheel, which is funded by the German Cancer Aid with 0.7 million euros, and a network on Parkinson research coordinated by the Center, which is led by Dr. Christian Johannes Gloor; this network is funded by the Michael J. Fox Foundation with 0.5 million U.S. dollars.

### ERC Grants at Helmholtz Zentrum München

<table>
<thead>
<tr>
<th>Number</th>
<th>Funding (in millions of euros)</th>
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<tbody>
<tr>
<td>Starting Grants [brought to the Center]</td>
<td>7 9.02 1 0.53</td>
</tr>
<tr>
<td>Consolidator Grants</td>
<td>2 3.85</td>
</tr>
<tr>
<td>Advanced Grants [as cooperation partner]</td>
<td>1 2.38 1 0.08</td>
</tr>
<tr>
<td>Total</td>
<td>12 15.9</td>
</tr>
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</table>
In 2012 and 2013 a total of 20 new projects were approved by the Initiative and Networking Fund (IVF) of the Helmholtz Association of German Research Centres:

The Helmholtz Alliance ICEMED (Imaging and Curing Environmental Metabolic Diseases), coordinated by Prof. Dr. Matthias Tschöp and including 18 partners, is being funded with a total of 15 million euros until 2017. Of these funds, four million euros are to remain at Helmholtz Zentrum München.

The Center is a partner in the Helmholtz Alliance Preclinical Comprehensive Cancer Center (PCCC), in the Helmholtz Alliance Remote Sensing and Earth System Dynamics and the special project Synthetic Biology, altogether funded with 0.8 million euros.

The Helmholtz Research School of Radiation Sciences (RS2) receives funding amounting to 1.8 million euros.

Four new Helmholtz Young Investigator Groups are to receive 625,000 euros each over five years.

In the framework of the Helmholtz Postdoctoral Program, three projects are to receive 100,000 euros each over three years, and two additional projects from the research field Health are to receive 150,000 euros each.

Within the framework of the W2/W3 program for women professors, Dr. Irmela Jeremias has received a W2 position to conduct research on “Diseases of the Immune System – Personalized Medicine Targeting Leukemia Stem Cells”.

Two Helmholtz International Research Groups at the Institute of Diabetes Research and the Institute of Lung Biology are being funded with 280,000 euros.

As part of the Helmholtz-Alberta Initiative “Infectious Diseases Research”, the Institute of Virology under the direction of Prof. Dr. Ulrike Protzer has been awarded 0.2 million euros for research projects.

Two of the Helmholtz International Fellow Awards, which are endowed with 20,000 euros each and were awarded for the first time in 2013, went to cooperation partners of Helmholtz Zentrum München: Prof. Dr. Harald von Boehmer of Harvard Medical School in Boston, and Prof. Dr. Naftali Kaminski of the University of Pittsburgh.

Dr. Jan Krumsiek, Institute of Computational Biology, has received the Helmholtz Doctoral Student Award in the research field Health, which is endowed with 5000 euros.

Helmholtz Zentrum München has close contacts with the two Munich universities and the Max Planck Institutes of Biochemistry and of Neurobiology. The success of this cooperation is shown in nine Collaborative Research Centres/Transregios of the German Research Foundation (DFG), in which Helmholtz Zentrum München participates with 34 subprojects. Along with Berlin, Munich plays a prominent role as cluster location for the life sciences in Germany.

For Helmholtz Zentrum München, projects funded by the German Research Foundation comprise an important component of the externally funded research activities. This especially applies to young, outstanding junior research group leaders, who are funded through the Emmy Noether Program of the DFG. In 2012/13 the Center established three new junior research groups with a total volume of more than 4.5 million euros through this funding program.

**Participation of Helmholtz Zentrum München in DFG-funded projects 2012/2013**

<table>
<thead>
<tr>
<th>Funding program</th>
<th>Projects</th>
</tr>
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<tbody>
<tr>
<td>7 Collaborative Research Centres and 2 Transregios</td>
<td>34</td>
</tr>
<tr>
<td>10 priority programs</td>
<td>13</td>
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<tr>
<td>7 research groups</td>
<td>7</td>
</tr>
<tr>
<td>Leibniz Prize</td>
<td>1</td>
</tr>
<tr>
<td>Junior research groups in the Emmy Noether Program</td>
<td>3</td>
</tr>
<tr>
<td>Individual grants</td>
<td>19</td>
</tr>
</tbody>
</table>

**International Cooperation**

In 2012/2013, Helmholtz Zentrum München participated in approximately 1200 international scientific collaborations with universities, non-university research institutions and industry partners in over 60 countries.

These partnerships may, but need not necessarily have a contractual basis. In 2013, there were more than 270 cases of international funding or cooperation agreements, often with multiple partners.

International cooperation serves the exchange between scientists on the basis of guest stays and collaborative research or publications. The U.S. tops the list by far in the number of non-European cooperative projects, followed by Canada, China and Japan. Within Europe, Center scientists collaborate particularly often with scientists from the UK, France, Italy, Austria, the Netherlands, Switzerland and Spain.

A special element of the Center’s international activities is the Helmholtz-Israel cooperation on personalized medicine, which was launched in 2013 and in which Helmholtz Zentrum München and four other biomedical Helmholtz centers and scientific institutions in Israel have joined together. The objective of the long-term cooperation is to develop new strategies for personalized medicine in the field of diagnosis, treatment and prevention of widespread common diseases such as diabetes.
In the fields of Environmental and Radiation Sciences, eleven institutes and research units have joined to form departments; five institutes comprise the Helmholtz Diabetes Center.
Institutes and Research Units

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**Mechanisms of Genetic and Environmental Influences on Health and Diseases**

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**DEPARTMENT OF RADIATION SCIENCES**
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Organization

Helmholtz Zentrum München is a research institution of the Federal Government and the Free State of Bavaria. The partners are the Federal Republic of Germany, represented by the Federal Minister of Education and Research, and the Free State of Bavaria, represented by the Bavarian State Minister of Finance, Regional Development and Regional Identity.

The bodies of the company are the Assembly of Partners, the Supervisory Board and the Board of Directors. The Scientific Advisory Board, which is made up of external members, advises Helmholtz Zentrum München on scientific issues. Scientists are represented in the Management Committee by the program and topic speakers. The Scientific Review Committee as expert body also advises the Board of Directors on important scientific matters.

### Members of the Board of Directors

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. Dr. Günther Wess</td>
<td>CEO</td>
</tr>
<tr>
<td>Dr. Alfons Enhsen</td>
<td>CTO</td>
</tr>
<tr>
<td>Dr. Nikolaus Blum</td>
<td>CFO</td>
</tr>
</tbody>
</table>

### Members of the Supervisory Board

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Ministry/Ministry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair</td>
<td>MinDir’in Bärbel Brumme-Bothe</td>
<td>Federal Ministry of Education and Research</td>
</tr>
<tr>
<td>Vice Chair</td>
<td>MDirig. Dr. Ronald Mertz</td>
<td>Bavarian State Ministry of Economic Affairs and Media, Energy and Technology</td>
</tr>
<tr>
<td>MinR Dr. Christian Greipl</td>
<td>Federal Ministry for the Environment, Nature Conservation and Nuclear Safety</td>
<td></td>
</tr>
<tr>
<td>MinR Ulrich Reithmann</td>
<td>Bavarian State Ministry of Finance, Regional Development and Regional Identity</td>
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</tbody>
</table>

MinR’in Maria Becker | Federal Ministry of Health

*As of June 2014* | Within the framework of the new Partnership Agreement, changes in the composition of the Supervisory Board are being made.*
Members of the Scientific Advisory Board

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
<th>Institution and Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair</td>
<td>Professor Hillel Koren</td>
<td>Environmental Health, LLC Durham, North Carolina, USA</td>
</tr>
<tr>
<td>Vice Chair</td>
<td>Professor Steve Brown</td>
<td>MRC Harwell, Harwell Science and Innovation Campus, Oxfordshire, UK</td>
</tr>
<tr>
<td></td>
<td>Professor Amnon Altman</td>
<td>Head, Division of Cell Biology, La Jolla Institute for Allergy &amp; Immunology, California, USA</td>
</tr>
<tr>
<td></td>
<td>Professor Elizabeth Fisher</td>
<td>UCL Institute of Neurology, London, UK</td>
</tr>
<tr>
<td></td>
<td>Professor Edda Klipp</td>
<td>Humboldt-Universität zu Berlin, Department of Biology, Germany</td>
</tr>
<tr>
<td></td>
<td>Professor Geoff J. Laurent</td>
<td>Centre for Cell Therapy and Regenerative Medicine, University of Western Australia, Nedlands, Australia</td>
</tr>
<tr>
<td></td>
<td>Professor Edward H. Leiter</td>
<td>The Jackson Laboratory, Bar Harbor, Maine, USA</td>
</tr>
<tr>
<td></td>
<td>Professor Urban Lendahl</td>
<td>Department of Cell and Molecular Biology (CMB), Karolinska Institutet, Stockholm, Sweden</td>
</tr>
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<td></td>
<td>Professor Stephanie J. London</td>
<td>National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA</td>
</tr>
<tr>
<td></td>
<td>Dr. Manfred Rösner</td>
<td>mroe-consulting, Eppstein, Germany</td>
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<td></td>
<td>Professor Sisko Salomaa</td>
<td>STUK, Radiation and Nuclear Safety Authority, Research and Environmental Surveillance, Helsinki, Finland</td>
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<tr>
<td></td>
<td>Professor Christine Foyer</td>
<td>Centre for Plant Sciences, University of Leeds, UK</td>
</tr>
<tr>
<td></td>
<td>Professor Bernhard Wehrli</td>
<td>ETH Zurich, Institute of Biogeochemistry and Pollutant Dynamics, Switzerland</td>
</tr>
<tr>
<td></td>
<td>Professor Stephen C. Woods</td>
<td>Department of Psychiatry, University of Cincinnati, Ohio, USA</td>
</tr>
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</table>
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