National Genome Research Network

1st Annual Meeting of

NGFN-Plus and NGFN-Transfer in the Program of Medical Genome Research

12th – 13th December 2008
Helmholtz Zentrum München

SPONSORED BY THE

Federal Ministry of Education and Research

HelmholtzZentrum münchen
German Research Center for Environmental Health

http://www.ngfn-meeting.de

Table of Contents

Welcome Remarks

Dear conference participant,

On behalf of the conference committee, we cordially welcome you at the

1st Annual Meeting of NGFN-Plus and NGFN-Transfer in the Program of Medical Genome Research 12th – 13th December 2008 at Helmholtz Zentrum München.

This conference convenes outstanding scientists in the field of medical genome research. The event offers the superb opportunity of information about the latest developments, presentation of scientific results, and discussion and interaction with most competent researchers in dynamic atmosphere.

With the *Program of Medical Genome Research*, the German Federal Ministry of Education and Research (BMBF) has launched a future-oriented new concept. Scientists from 26 Integrated Consortia, which are organized in the program partition *NGFN-Plus*, are presenting their projects and novel results these days at HMGU. A wide panel of disease areas causative for high individual and social burdens and thus most relevant for health policy is investigated in these consortia with use of novel technologies. The eight Innovation Alliances in the new program partition *NGFN-Transfer* present their innovative approaches to transfer results from medical genome research into medical application.

The enormous diversity of NGFN is presented in six symposia of the topics *Genomics of Common Disease*, *Systems Biology*, *Genome Regulation*, *Animal, Cellular & Tissue Models*, *Genomic-Environmental Interaction*, and *Transfer from Genomics to Application*. Internationally renowned keynote speakers will open each session with an overview. Scientists of the NGFN will then present latest results.

Already in the run-up of the conference, two workshops focus on most relevant topics: *Next-Generation Sequencing* and *The NGFN GWAS Program for Complex Phenotypes.* The presentation of novel results by employing powerful cutting-edge technology will demonstrate impressive results in medical genome research.

To all six symposia the conference offers poster sessions. In order to motivate young scientists, to strengthen the importance of the poster presentation, and in memory of the late Prof. Dr. Annemarie Poustka, three posters will receive the "Annemarie Poustka Poster Award for Medical Genome Research" sponsored by Roche Diagnostics. Annemarie Poustka made outstanding achievements in the field of Genome Research in general and was a visionary scientist for the NGFN in particular.

The program is rounded up by company satellite lunch sessions and an industrial exposition offering comprehensive information on latest technology development in supply relevant for researchers of the network.

To all members of NGFN-Plus and NGFN-Transfer, this is a unique chance for a first get-together within the novel BMBF Program for Medical Genome Research. We are delighted to welcome many members of NGFN-2, all those scientists that are interested in the program as well as all further visitors of our conference. You are invited to take actively part in the flow of information and the opportunity to meet new and "old" collaborators and to reinforce existing co-operations.

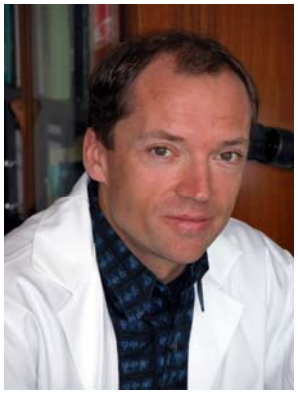
Last but not least, don't miss the social highlight on Friday evening and meet with the scientific community for a relaxed ambience, delicious dinner and great music!

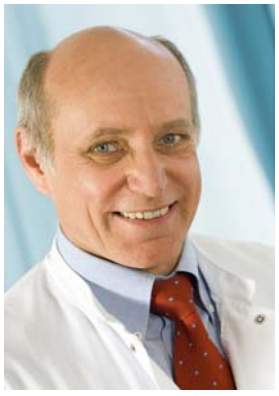
Munich and Heidelberg, Dec. 4, 2008

Prof. Martin Hrabé de Angelis

Prof. Hugo Katus

(As Spokespersons for the Project Committee of NGFN-Plus and NGFN-Transfer in the Program of Medical Genome Research)





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DKFZ Heidelberg

Prof. Wolfgang Wurst
Helmholtz Zentrum München

Program-at-a-glance

Thursday, December 11th

1:00 – 4:00 pm	**Workshop: Next Generation Sequencing**
4:00 – 4:30 pm	***Coffee Break***
4:30 – 8:00 pm	**Workshop: The NGFN Genome-Wide Association Studies (GWAS) Program for Complex Phenotypes**
8:00 pm	***Supper***

Friday, December 12th

8.30 – 9:00 am	**Welcome:** **Günther Wess**, Scientific Director, HMGU **Elmar Nimmesgern**, BMBF **Martin Hrabé de Angelis**, Speaker Project Committee of NGFN-Plus / NGFN-Transfer in the Program of Medical Genome Research
9:00 - 11.15 am	**Symposium I – Genomics of Common Disease** Nilesh Samani (Keynote) – Arne Pfeufer – Marcella Rietschel – Sven Cichon – Iris Heid – André Franke – Thomas Illig
11:45 – 1:00 pm	**Symposium II – Systems Biology** Ralf Herwig (Keynote) – Vinayagam Arunachalam – Lars Dölken – Holger Fröhlich
1:00 – 3:45 pm	***Lunch Break and Poster Session I-IV***
1:00 – 3:45 pm	**Company Satellite Lunch Sessions** Roche Diagnostics GmbH – Illumina Ltd – Applied Biosystems - Affymetrix
3:00 – 4:45 pm	**Symposium III – Genome Regulation** Martin Vingron (Keynote) – Matthias Selbach – Jörg Hoheisel – Johannes Schulte – Jochen Supper
5:15 – 7:00 pm	**Symposium IV – Animal, Cellular & Tissue Models** Howard Jacob (Keynote) – Stefan Wiemann – Jan Rozmann – Ildikó Rácz – Benjamin Meder
7:00 – 8:00 pm	**Evening Lecture** Matthias Mann

8:00 pm - open end: ***Get-Together & Dinner***

Saturday, December 13th

9:00 - 10.45 am	**Symposium V – Genomic / Environmental Interaction** Cornelia M. van Duijn - Christian Gieger – Tobias Stoeger – Rainer Spanagel – Hadi Al-Hasani
10:45 – 12:45 pm	***Lunch Break and Poster Session II – Posters Symposia V-VI***
10:45 – 12:45 pm	**Company Satellite Lunch Sessions:** Roche Diagnostics GmbH – Illumina Ltd – TMF e.V.
12:45 – 2:30 pm	**Symposium VI: Transfer from Genomics to Application** Bert Klebl (Keynote) – Martin Sos – Eva Lattka – Nicole Huebener – Michal-Ruth Schweiger
2:30 – 2:45 pm	**Competence Center Technology Transfer (KTT)** Isabel von Korff
2:45 – 3:00 pm	**Ceremony: "Anemarie Poustka Poster Award of Medical Genome Research" sponsored by Roche Diagnostics GmbH** **Concluding Remarks:** Hugo Katus, Speaker Project Committee of NGFN-Plus/NGFN-Transfer in the Program of Medical Genome Research

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HelmholtzZentrum München

Workshop
The National Genome Research Network (NGFN)
Next Generation Sequencing (NGS) Program
December 11th 2008

Scientific Organization: Dr. Richard Reinhardt

Welcome and overview of related BMBF projects		**Chair: Dr. Bernhard Korn**
1:00 pm	Introduction	Dr. Richard Reinhardt
Session 1, New System Developments and Updates		**Chair: Richard Reinhardt**
1:10 pm	Genome Analyser II	Dr. Richard Henfrey Illumina
1:20 pm	SOLiD™3 : Application Range and Technology development	Dr. Thomas Rygus Applied Biosystems
1:30 pm	The Genome Sequencer FLX powered by 454 sequencing	Dr. Marcus Droege Roche
Session 2, IT platform development and organization at the MPI Berlin-Dahlem		**Chair: Richard Reinhardt**
1:40 pm		Peter Marquardt, Berlin
1:50 pm – 2:00 pm	**Discussion**	

Session 3, Commercial service partner / application offer		**Chair: Richard Reinhardt**
2:00 pm	AGOWA	Dr. Wolfgang Zimmermann AGOWA
2:10 pm	GATC	Dr. Christopher Bauser GATC
2:20 pm	MWG-Eurofins	Dr. Georg Gradl MWG-Eurofins
Session 4, Academic service partner / application offer		**Chair: Richard Reinhardt**
2:30 pm	Genome Analyzer II platform-Berlin	Dr. Bernd Timmermann MPI-MG, Berlin
2:40 pm	SOLiD platform – Kiel	Dr. Markus Schilhabel University Kiel
2:50 pm	454 platform – Heidelberg	Dr. Bernhard Korn DKFZ, Heidelberg

3:00 pm – 3:10 pm **Discussion**

Session 5, Sample Enrichment / Capture		**Chair: Bernhard Korn**
3:10 pm	Agilent / ImaGenes	Dr. Christoph Koenig
3:20 pm	biomed platform / Febit	Dr. Nadine Schracke
3:30 pm	NimbleGen platform / Roche	Dr. Heike Fiegler

3:40 pm – 3:50 pm **Discussion**

Summary, further organization, outlook and new offer for workshops
Chair: Bernhard Korn

3:50 pm – 4:00 pm Concluding remarks — Dr. Richard Reinhardt

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Workshop
The National Genome Research Network (NGFN)
Genome-Wide Association Studies (GWAS)
Program for Complex Phenotypes

December 11th 2008

Scientific Organization: Prof. Dr. Stefan Schreiber

4.30 pm	Introduction	Stefan Schreiber
4.40 pm	Data Cleaning and Management	Thomas Wienker

Session 1, CNS Disorders — **Chair: Thomas Wienker** (Max Baur)

4.50 pm	Adipositas	Anke Hinney (J. Hebebrand)
4.55 pm	Bipolar Affective Disorder	Sven Cichon (J. Schumacher, P. Propping)
5.00 pm	Schizophrenia	Sven Cichon (M. Rietschel, P. Propping)
5. 05 pm	Alcohol Addiction	Sven Cichon (R. Spanagel)
5.10 pm	Unipolar Affective Disorder	Susanne Lucae
5.15 pm	Parkinson's Disease	Thomas Gasser
5.20 pm	Alzheimer's Disease	Thomas Gasser (M. Riemenschneider)
5.25 pm	Epilepsy	Thomas Sander

Session 2, Inflammatory Diseases **Chair: Thomas Wienker** (Max Baur)

5.30 pm	Crohn's Disease	André Franke (S. Schreiber)
5.35 pm	Ulcerative Colitis	André Franke (S. Schreiber)
5.40 pm	Psoriasis	André Franke (M. Weichenthal)
5.45 pm	Primary Sclerosing Cholangitis	André Franke
5.50 pm	Acute Lymphoblastic Leukemia	André Franke
5.55 pm	Atopic Eczema	Young-Ae Lee (S. Weidinger, A. Ruether)
6.00 pm	Sarcoidosis	Sylvia Hofmann
6.05 pm	Malaria	Rolf Horstmann
6.10 pm	Tuberculosis	Rolf Horstmann (Ch. Meyer)

Coffee Break 6.15 pm – 6.30 pm

Session 3, Cardiovascular Diseases **Chair: Stefan Schreiber**

6.30 pm	Left Ventricular Hypertrophy	Hugo Katus (N. Frey)
6.35 pm	Diastolic Myocardial Insufficiency	Hugo Katus (G. Hasenfuß)
6.40 pm	Dilatative Cardiomyopathy	Hugo Katus (B. Ivandic)
6.45 pm	Coronary Heart Disease / Ostium Stenosis	Hugo Katus (J. Erdmann)
6.50 pm	Human Life Expectancy	Almut Nebel (S. Schreiber, F. Flachsbart)
6.55 pm	Periodontitis (co-funded by DFG)	Stefan Schreiber (A. Schäfer)

Session 4, Data derived from population studies **Chair: Stefan Schreiber**

7.00 pm	Popgen	Michael Nothnagel (M. Krawczak)
7.05 pm	KORA	H.-Erich Wichmann

Break 7.10 pm – 7.20 pm

7.20 – 7.30 pm	Next steps, Joint Analysis	Stefan Schreiber
7.30 – 8.00 pm	**Discussion**	

Program

Thursday, December 11th, 2008

1:00 – 4:00 pm	**Workshop: Next Generation Sequencing**
4:00 – 4:30 pm	***Coffee Break***
4:30 – 8:00 pm	**Workshop: The NGFN Genome-Wide Association Studies (GWAS) Program for Complex Phenotypes**
8:00 pm	***Supper***

Friday, December 12th, 2008

8:30 – 9:00 am **Welcome:**

Günther Wess, Scientific Director, HMGU

Elmar Nimmesgern, BMBF

Martin Hrabé de Angelis, Speaker Project Committee of NGFN-Plus / NGFN-Transfer in the Program of Medical Genome Research

Symposium I: Genomics of Common Disease

(Chairs: Hugo Katus, Stefan Schreiber)

9:00 – 9:45 am	**Keynote: Nilesh Samani**, University of Leicester, UK *Genetics of CAD (coronary artery disease): an update*
9:45 – 10:00 am	**Arne Pfeufer,** Institute of Human Genetics, Technical University Munich & Helmholtz Zentrum München, Germany *Common variants at ten loci modulate the QT interval duration in individuals of European ancestry: the QTSCD consortium*
10:00 – 10:15 am	**Marcella Rietschel**, Central Institute of Mental Health Mannheim, Germany *Genome-wide association study of alcohol dependence*
10:15 – 10:30 am	**Sven Cichon,** Life & Brain Center, University of Bonn, Germany *Large recurrent microdeletions associated with schizophrenia*
10:30 – 10:45 am	**Iris Heid,** Helmholtz Zentrum München, Germany *Meta-analyses of genome-wide association studies: six new obesity associated loci highlight a neuronal influence on body weight regulation*
10:45 – 11:00 am	**André Franke,** Center for Statistical Genetics, MI, USA *Genome-wide scan reveals association of psoriasis with IL-23 and NF-kB pathways*
11:00 – 11:15 am	**Thomas Illig,** Helmholtz Zentrum München, Germany *Genome-wide scan on total serum IgE levels identifies FCER1A as novel susceptibility locus*
11:15 – 11:45 am	***Coffee Break***

Symposium II: Systems Biology

(Chairs: Hans Lehrach, Hans-Werner Mewes)

11:45 – 12:15 pm	**Keynote: Ralf Herwig**, Max Planck Institute for Molecular Medicine Berlin, Germany *Integration of human molecular interactions*
12:15 – 12:30 pm	**Vinayagam Arunachalam,** Max Delbrück Center Berlin, Germany *Constructing a causal protein interaction network for activated MAPK signalling*
12:30 – 12:45 pm	**Lars Dölken,** Max von Pettenkofer-Institute Munich, Germany *High resolution gene expression profiling for simultaneous kinetic parameter analysis of RNA synthesis and decay*
12:45 – 1:00 pm	**Marc Johannes,** DKFZ (German Cancer Research Center) Heidelberg, Germany *Predicting pathway membership via domain signatures*
1:00 – 3:00 pm	***Lunch Break and Poster Session I - Posters Symposia I-IV***
1:00 – 3:00 pm	**Company Satellite Lunch Sessions:** **Roche Diagnostics GmbH** – *1) Cell Analyser xCELLigence* *2) High Throughput Sequencing with the New Titanium Reagents.* **Illumina Ltd** – *Integrative Genetics and Next Generation Sequencing Tools by Illumina* **Applied Biosystems GmbH** – *Ultra High Throughput sequencing analysis of Transcriptome in single cells with SOLiD 3 System* **Affymetrix –** *New Developments for high throughput genotyping and integrated Expression analysis*

Symposium III: Genome Regulation

(Chairs: Angelika Eggert, Peter Lichter)

3:00 – 3:45 pm	**Keynote: Martin Vingron**, Max Planck Institute for Molecular Genetics, Berlin, Germany *Computational Regulatory Genomics*
3:45 – 4:00 pm	**Matthias Selbach**, Max Delbrück Center Berlin, Germany *Genome-wide identification of microRNA targets by pulsed stable isotope labelling (pSILAC)*
4:00 – 4:15 pm	**Jörg Hoheisel,** DKFZ (German Cancer Research Center) Heidelberg, Germany *Looking at microRNA and mRNA profiles and related epigenetic variations in promoter regions of pancreatic cancer samples*
4:15 – 4:30 pm	**Johannes Schulte,** Universitätskinderklinik Essen, Germany *Histone demethylase LSD1 is highly expressed in poorly differentiated neuroblastoma and is a novel therapeutic target*
4:30 – 4:45 pm	**Jochen Supper,** Center for Bioinformatics Tübingen, Germany *Predicting DNA-binding specificities of transcription factors*
4:45 – 5:15 pm	***Coffee Break***

Symposium IV: Animal, Cellular & Tissue Models

(Chairs: Stefan Wiemann, Wolfgang Wurst)

5:15 – 6:00 pm	**Keynote: Howard Jacob**, Medical College Wisconsin, Milwaukee, USA *The Role of Transgenic Rats in a Genome Wide Association Studies (GWAS) World*
6:00 – 6:15 pm	**Stefan Wiemann**, DKFZ (German Cancer Research Center) Heidelberg, Germany *IG-CSG- cellular systems genomics*
6:15 – 6:30 pm	**Jan Rozman,** Helmholtz Zentrum München & Technical University München, Germany *Identification of new targets playing a role in metabolic diseases by systemic analysis in the German Mouse Clinic*
6:30 – 6:45 pm	**Ildikó Rácz,** University of Bonn, Germany *Modulation of neuropathic pain by endocannabinoids*
6:45 – 7:00 pm	**Benjamin Meder,** University of Heidelberg, Germany *Myosin light chain-1 controls cardiac contractility*

Evening Lecture:

7:00 – 8:00 pm	**Matthias Mann,** MPI of Biochemistry, Martinsried, Germany *High resolution proteomics in functional genomics*
8:00 pm - open end:	***Get-Together, Dinner***

Saturday, December 13th, 2008

Symposium V: Genomic / Environmental Interaction

(Chairs: Markus Nöthen, H.-Erich Wichmann)

9:00 – 9:45 am	**Keynote: Cornelia M. van Duijn**, Erasmus University Medical School, Rotterdam, Netherlands *From genome wide association studies to risk prediction: the importance of studies of gene interactions*
9:45 – 10:00 am	**Christian Gieger,** Helmholtz Zentrum München, Germany *Genetics meets metabolomics: a genome-wide association study of metabolite profiles in human serum*
10:00 – 10:15 am	**Tobias Stoeger,** Helmholtz Zentrum München, Germany *Response to ultrafine particle instillation in two mouse strains with extremely divergent lung function*
10:15 – 10:30 am	**Rainer Spanagel,** Central Institute of Mental Health Mannheim, Germany *Alcoholism – A Systems approach from molecular physiology to addictive behaviour*
10:30 – 10:45 am	**Hadi Al-Hasani,** German Institute for Human Nutrition Nuthetal, Germany *Tbc1d1 mutation confers leanness and protects from diet-induced obesity and diabetes*
10:45 – 12:45 pm	***Lunch Break and Poster Session II – Posters Symposia V-VI***

10:45 – 12:45 pm	**Company Satellite Lunch Sessions:**
	Roche Diagnostics GmbH – *LightCycler 480 System (Real-Time PCR)*
	Illumina Ltd – *Genotyping and Gene-expression updates from Illumina*
	TMF e.V. – *Contact partner and common platform for networked medical research*

Symposium VI: Transfer from Genomics to Application

(Chairs: Markus Hecker, Birte Sönnichsen)

12:45 – 1:30 pm	**Keynote: Bert Klebl**, Lead Discovery Center GmbH, Dortmund, Germany *From genomes to drugs*
1:30 – 1:45 pm	**Martin Sos,** Max Planck Institute for Neurological Research Cologne, Germany *Defining PI3-Kinase dependency in non-small cell lung cancer*
1:45 – 2:00 pm	**Eva Lattka,** Helmholtz Zentrum München, Germany *Functional impact of polymorphisms on the human delta-6 desaturase gene promoter*
2:00 – 2:15 pm	**Nicole Huebener,** Charité – University Medicine Berlin, Germany *Xenogeneic immunization with human tyrosine hydroxylase DNA vaccines effectively eradicates established neuroblastoma and induces long lasting protective immunity*
2:15 – 2:30 pm	**Michal-Ruth Schweiger,** Max Planck Institute for Molecular Genetics, Berlin, Germany *High-throughput sequencing of snap frozen and paraffin embedded cancer and normal tissues*
2:30 – 2:45 pm	**Isabel von Korff,** Competence Center Technology Transfer (KTT) *Technology transfer in the program for medical genome research*
2:45 – 3:00 pm	**Ceremony:** "**Annemarie Poustka Poster Award of Medical Genome Research" sponsored by Roche Diagnostics GmbH**
	Concluding Remarks: Hugo Katus, Speaker Project Committee of NGFN-Plus / NGFN-Transfer in the Program of Medical Genome Research

Program

Thursday, December 11th, 2008

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8:00 pm	***Supper***

Friday, December 12th, 2008

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Symposium I: Genomics of Common Disease

(Chairs: Hugo Katus, Stefan Schreiber)

9:00 – 9:45 am ***Opening Keynote Presentation***

Genetics of CAD (coronary artery disease): an update
Nilesh Samani, University of Leicester, UK

Nilesh Samani is British Heart Foundation Professor of Cardiology and Head of the Department of Cardiovascular Sciences at the University of Leicester and Consultant Cardiologist at the Cardiac Centre, Glenfield Hospital, Leicester, UK. He graduated from the University of Leicester Medical School in 1981.

Dr Samani's main research interests are focused around understanding the inherited basis of common cardiovascular diseases, especially coronary artery disease and hypertension. He is a principle investigator on several national and international programmes on cardiovascular genetics including the Wellcome Trust Case Control Consortium, the British Genetics of Hypertension (BRIGHT) Study, the British Family Heart Study, and the European *Cardiogenics*, *Bloodomics* and ENGAGE integrated projects.

Professor Samani is a Fellow of the Academy of Medical Sciences of the United Kingdom and holds international fellowships of the American College of Cardiology and the American Heart Association.

9:45 – 10:00 am

Common variants at ten loci modulate the QT interval duration in individuals of European ancestry: the QTSCD consortium
Arne Pfeufer

Arne Pfeufer, MD MSc (*1966) obtained his masters degree in biochemistry in 1992 at Hannover University and his medical degree in 1997 at Humboldt University Berlin. In his medical thesis he characterized causal and modifier genes in hypertrophic cardiomyopathy. Between 1998 and 2000 he did residency training in medicine at the Charité in Berlin and the Kerckhoff-Klinik in Bad Nauheim where he continued to work on genetically determined cardiovascular disease. In 2001 he started his specialty training in human genetics at the Department of Human Genetics at the Klinikum Rechts der Isar, TU München. There he shifted his scientific interest more towards common genetic determinants and common heart diseases. Today his group is focused on complex cardiovascular phenotypes identifiying genetic variants predisposing to atrial fibrillation, long-QT syndrome and sudden cardiac death. His research is in close collaboration with the Medizinische Klinik I of the Klinikum der LMU München-Großhadern. A specific focus of his work is on quantitative traits from the EKG in the general population and in cardiac patients (e.g. QT-interval, PQ-interval and heart rate). As many of these are well-established epidemiologic risk factors for morbidity and mortality they are well suited to be studied as intermediate phenotypes in genetic research. His work led to the identification of the previously unknown association between the NOS1AP gene and cardiac repolarization in 2006 by an early genome-wide association study. In the meantime as part of a large international collaboration nine further QT-related quantitative trait loci have been identified, some of which are now emerging to be associated also with predisposition to sudden cardiac death.

10:00 – 10:15 am

Genome-wide association study of alcohol dependence
Marcella Rietschel

Professor Marcella Rietschel MD is a Professor of Psychiatry and Psychotherapy and a Medical Geneticist. She has been Head of the Department of Genetic Epidemiology in Psychiatry at the Central Institute of Mental Health in Mannheim, University of Heidelberg since 2002. Her research focus is the identification of genetic and environmental causes of mental disorders and their response to treatment, with an emphasis on affective, schizophrenia-spectrum and addiction disorders. Her department has a fully equipped molecular genetic laboratory and conducts extensive phenotype characterizations and the genotyping of affected individuals and their families using large internationally collected samples. Marcella Rietschel studied Medicine in Marburg, Germany and received her medical Degree and license to practice in 1984. She worked as a research fellow from 1984 until 1988 at the Department of Surgery at the University of Marburg, completing her thesis 'Seroepidemiologic Studies of Ebola- and Marburg-Virus Antibodies in Human Sera from Africa' at the Medical Centre of Hygiene and Medical Micobiology, Division of Virology. In 1988 she moved to the University of Bonn where she worked as a research fellow at the Institute of Human Genetics with Professor

Peter Propping until 1991. From 1991 until 1995 she trained in neurology and psychiatry in the Departments of Neurology and Psychiatry in Bonn and then worked as a consultant psychiatrist at the Department of Psychiatry in Bonn with Prof. Wolfgang Maier until moving to Mannheim in 2002. In 2000 she received her Habilitation (postdoctoral lecturer qualification) for her work "Identification of the influence of genetic variants of central nervous expressed genes on the etiology of disorder and individual pharmaco-response. Investigation of patients affected with bipolar-affective disorder and schizophrenia".

10:15 – 10:30 am

Large recurrent microdeletions associated with schizophrenia
Sven Cichon

Sven Cichon studied Biology at the University of Bonn and graduated in 1995 with a doctorate on the identification of genetic variability in CNS-expressed receptor/transporter genes and investigation of their impact for the development of neuropsychiatric disorders. During his post-doc time at the Institute of Human Genetics, University of Bonn, and at Millennium Pharmaceuticals Inc., Cambridge, MA, USA, his activities focused on disease gene identification for monogenic as well as genetically complex human diseases. Between 2001 and 2004, Dr. Cichon worked at the Department of Medical Genetics, University of Antwerp, Belgium, where he led a research group on psychiatric genetics. He returned to Bonn in 2004 to become Head of the Molecular Genetics Laboratory of the Department of Genomics at Life & Brain, a center of excellence in the field of translational biomedicine. The focus of his current research is on genomics strategies to unravel the molecular basis of complex diseases.

10:30 – 10:45 am

Meta-analyses of genome-wide association studies: six new obesity associated loci highlight a neuronal influence on body weight regulation
Iris Heid

Dr. Iris Heid has a degree in mathematics, a PhD in human biology on the topic of measurement error models for radon exposure at the medical faculty of the Ludwig-Maximilians-Universität München, and has submitted her Habilitation in the area of Genetic Epidemiology. Before her PhD, she worked at the Mayo Clinic, Cancer Center Statistics, in Rochester, MN, USA, and further two years as systems analyst in the industry. Since 1998, she is scientific staff member at the Institute of Epidemiology, Helmholtz Zentrum München, and heads a group of genetical statisticians since several years. A scientific focus is not only the investigation of genotyping error, but predominantly the identification and characterisation of genetic factors for obesity and related parameters, particularly by the means of genome-wide association studies and meta-analyses.

10:45 – 11:00 am

Genome-wide scan reveals association of psoriasis with IL-23 and NF-kB pathways

André Franke

Dr. Andre Franke was born in El Paso (Texas) in 1978. After studying Biology and Informatics in Kiel, he did his Diploma work in the field of Developmental Biology in the laboratory of Prof. Dr. Dr. Bosch. For his PhD work, he joined the group around Prof. Dr. Schreiber at the Institute for Clinical Molecular Biology and when receiving his degree in 2006, he became the head of the genetics and bioinformatics group within the institute of Prof. Dr. Schreiber. Since August this year, Dr. Franke is a Juniorprofessor for "Epithelial Barrier Diseases" within the excellence cluster "Inflammation at Interfaces". Prof. Dr. Franke has helped to identify several disease genes for various complex diseases and he was the first to describe genetic susceptibility factors for ulcerative colitis, a common sub-phenotype of chronic inflammatory bowel disease. His main interests are the development and establishment of novel ultra-high-throughput technologies and the inherent bioinformatic integration.

11:00 – 11:15 am

Genome-wide scan on total serum IgE levels identifies FCER1A as novel susceptibility locus

Thomas Illig

Thomas Illig studied Molecular Biology and earned his doctorate at the University of Regensburg. Afterwards he went as PostDoc to the GSF Research Center for Environment and Health now Helmholtz Zentrum München (HMGU). In 2001 he was appointed to the leader of the working group "Molecular Epidemiology" in the Institute of Epidemiology (HMGU) where he is still working today. In 2006 Thomas Illig qualified as a professor in the field of Public Health at the Ludwig-Maximilians-University Munich.The last years he specialized on biobanking especially of the KORA cohort, genotyping and metabolomic analyses. His main scientific interest is the molecular analysis of complex diseases like type 2 diabetes, obesity and allergic diseases.

11:15 – 11:45 am ***Coffee Break***

Symposium II: Systems Biology

(Chairs: Hans Lehrach, Werner Mewes)

11:45 – 12:15 pm ***Opening Keynote Presentation***

Integration of human molecular interactions
Ralf Herwig

Ralf Herwig has studied Mathematics and Physics at the Technical and Free Universities of Berlin and did his PhD on clustering algorithms for large gene expression data sets at the Max Planck Institute for Molecular Genetics in Berlin. Since 2001 he is group leader of the bioinformatics group at the Department of Vertebrate Genomics. The bioinformatics group develops algorithms and resources for genome and proteome research, databases and data integration systems as well as systems biology resources. The group is involved in several EU and BMBF projects and is integrated in international data and database standardisation efforts. Ralf Herwig participates in several NGFN projects such as the NGFN-plus projects MUTANOM on systems genetics of cancer and MODIFIERS on modifiers of intestinal tumor formation and progression as well as the NGFN-transfer project "New Tools for the Prevention of Cardiovascular Diseases and Disorders in Chronic Kidney Disease".

12:15 – 12:30 pm ***Constructing a causal protein interaction network for activated MAPK signalling***

Vinayagam Arunachalam

Dr. Vinayagam Arunachalam obtained his masters in Microbiology from Bharathidasan University, India. He carried out his Ph.D in computational biology at the German Cancer Research Center (DKFZ), Heidelberg. He is currently a post-doctoral fellow at the Max-Delbrueck Center for Molecular Medicine, Berlin. He began his research career in the field of protein fold recognition, where he has developed a novel fold recognition method for small disulphide rich peptides. During his Ph.D he has developed an automated method for large-scale gene function prediction, which has also been published as a monograph. His current research interests are applying protein-protein interaction networks to understand cellular signaling and predicting disease modulators. Specifically, he is interested in predicting potential modulators of Huntington's disease, a neurodegenerative disorder. Further, he has also created a human casual protein interaction network to explore cellular signaling pathways.

12:30 – 12:45 pm

High resolution gene expression profiling for simultaneous kinetic parameter analysis of RNA synthesis and decay
Lars Dölken

After studying medicine at the University of Greifswald (Germany) and Otago (New Zealand) Lars Dölken started as a post-doctoral fellow in Prof. U.H. Koszinowski's lab at the Max von Pettenkofer-Institute in Munich. His research is focussed on miRNAs of various herpesviruses, in particular of the murine cytomegalovirus (MCMV) as the standard animal model used to study the biology of cytomegalovirus infection in vivo. Another focus of his group is the development and application of novel RNA labeling techniques for high resolution gene expression profiling of RNA synthesis and decay.

12:45 – 1:00 pm

Predicting pathway membership via domain signatures
Marc Johannes

Marc Johannes studied Bioinformatics at the University of Applied Sciences in Bingen. After obtaining his *Diplom* he worked from 2007-2008 as a bioinformatics software developer at the biotech company *febit biomed gmbh*. Since summer 2008 he works as a PhD student in the *Bioinformatics and Modeling* group within the division of *Molecular Genome Analysis* at *DKFZ*.

He is working on the analysis of *Affymetrix Exon-Array* data and on machine learning tasks within the NGFN project IG-Prostate Cancer of PD Dr. Holger Sültmann. The work presented here was performed in collaboration with Dr. Holger Fröhlich in the IG-Systems Genomics of PD Dr. Stefan Wiemann and with Prof. Dr. Tim Beißbarth (subproject leader).
Reference: H. Fröhlich et al. *Predicting pathway membership via domain signatures.* Bioinformatics, 2008.

1:00 – 3:00 pm

Lunch Break and Poster Session I - Posters Symposia I-IV

1:00 – 3:00 pm

Company Satellite Lunch Sessions:

Roche Diagnostics GmbH
1) Cell Analyser xCELLigence
2) High Throughput Sequencing with the New Titanium Reagents

Illumina Ltd
Integrative Genetics and Next Generation Sequencing Tools by Illumina

Applied Biosystems GmbH
Ultra High Throughput sequencing analysis of Transcriptome in single cells with SOLiD 3 System

Affymetrix
New Developments for high throughput genotyping and integrated Expression analysis

Symposium III: Genome Regulation

(Chairs: Angelika Eggert, Peter Lichter)

3:00 – 3:45 pm

Opening Keynote Presentation

***Computational Regulatory* Genomics**
Martin Vingron

Martin Vingron is a director at the Max Planck Institute for Molecular Genetics and honorary professor for computer science at Free University Berlin. He studied mathematics in Vienna, Austria, and received his PhD in mathematics in 1991 from Heidelberg University for work done at EMBL. After two postdocs in Los Angeles and Bonn he became head of the Theoretical Bioinformatics Division at Deutsches Krebsforschungszentrum (DKFZ). In 2000 he moved to the MPI in Berlin. Vingron was awarded the Max Planck Research Prize in 2004 and is a member of the German Academy of Sciences Leopoldina.

3:45 – 4:00 pm

Genome-wide identification of microRNA targets by pulsed stable isotope labelling (pSILAC)
Matthias Selbach

Matthias Selbach studied biology at the University of Muenster (Germany). He then moved to the Max Planck Institute of Infection Biology in Berlin where he received his PhD in 2003 for work on cell signaling elicited by bacterial pathogens. In 2004 he went to the lab of Matthias Mann in Odense (Denmark) and followed him to the Max Planck Institute of Biochemistry (Munich). Being a postdoctoral fellow in a renowned proteomics lab, quantitative mass spectrometry rapidly became a cornerstone of his work. For example, Matthias used proteomics to study the *in vivo* metabolism of *Salmonella* during infection. He also developed the first screening method for endogenous protein-protein interactions. Since 2007 Matthias heads an independent junior research group (tenure track) at the Max Delbruck Center for Molecular Medicine in Berlin. Major research interests of his lab are cellular signal transduction networks, posttranscriptional regulation of gene expression and protein-protein interaction.

4:00 – 4:15 pm

Looking at microRNA and mRNA profiles and related epigenetic ***variations in promoter regions of pancreatic cancer samples***
Jörg Hoheisel

Jörg D. Hoheisel is Head of the *Division of Functional Genome Analysis* at the Deutsches Krebsforschungszentrum (DKFZ; German Cancer Research Centre) in Heidelberg, Germany. He is currently particularly active in the area of establishing and applying mostly global analysis techniques at the levels of DNA, RNA and proteins – with some emphasis on array-based assays – for the examination, evaluation and experimental modelling of molecular cellular functions. Concerning the analysis of human material, biomedical systems are being developed toward early diagnosis, prognosis, identification of new therapy approaches and evaluation of treatment success. Biologically, his

scientific interests are in the areas of structure, organisation and interaction of the different molecule classes and the resulting regulative aspects. Apart from publications in scientific journals, the division filed a large number of patents, of which quite a few have been licensed to companies or are utilised in ongoing collaborations with commercial partners.

Prior to joining DKFZ in 1993, he worked for five years on genome-wide analyses and technical developments in this research field in the group of Hans Lehrach at the Imperial Cancer Research Fund in London, UK, the initial two years being funded by a post-doctoral EMBO fellowship.
Previously, he had been trained as a molecular biologist at the University of Constance, Germany. He did his diploma graduation and Ph.D. degree with Fritz M. Pohl at the Department of Physical Biochemistry on the subjects of analysing different, topologically induced DNA-structures and the functioning of DNA-binding enzymes.

4:15 – 4:30 pm

Histone demethylase LSD1 is highly expressed in poorly differentiated neuroblastoma and is a novel therapeutic target
Johannes Schulte,

Johannes Schulte is Paediatric Resident at the University Children's Hospital Essen, Germany and Scientist at their Department of Paediatric Oncology and Haematology since November 2006.

He was previously Resident in Pathology at the University of Bonn (January - October 2006).
In 2005 he graduated from Medical School, University of Essen and passed his Doctoral Thesis at the Department of Paediatric Oncology

Awards: Astra Zeneca Scholar in Training Award (Oncogenomics) 2001
ANR Young Investigator Research Fellowship 2006
Award of the 'Wiedenfeld Stiftung' for Cancer Research 2007
Memberships: AACR Associate Me
Grants:
Bundesministerium für Bildung und Forschung (BMBF), NGFNplus "Extended Neuroblastoma Genome Interaction NEtwork (ENGINE)", Principle investigator for the work package,"Transposon mutagenesis screen in mice to uncover the genetic basis of neuroblastoma and to identify neuroblastoma-initiating genes"

Bundesministerium für Bildung und Forschung (BMBF), NGFNplus "Extended Neuroblastoma Genome Interaction NEtwork (ENGINE)", Principle investigator for the work package, "The Pathogenetic Role and Therapeutic Potential of microRNAs in NB"

4:30 – 4:45 pm ***Predicting DNA-binding specificities of transcription factors***
Jochen Supper

Jochen Supper studied bioinformatics at the University of Tübingen and the University of Washington. In 2005, he started his PhD at the Center for Bioinformatics Tübingen (ZBIT) under Prof. Zell. In 2007, he worked under Prof. Bonneau as visiting scientist at the New York University (NYU). Currently, he is finishing his thesis entitled: "Computational inference of gene regulatory networks". Within this thesis he developed a workflow to infer gene regulatory interactions by: biclustering multi-conditioned gene expression datasets, finding enriched transcription factor binding sites and modules, and modeling gene regulatory interactions. Jochen Supper's scientific interests include the analysis of -omics datasets, data integration, statistical analysis, and all types of regulatory networks within cells."

4:45 – 5:15 pm ***Coffee Break***

Symposium IV: Animal, Cellular & Tissue Models

(Chairs: Stefan Wiemann, Wolfgang Wurst)

5:15 – 6:00 am ***Opening Keynote Presentation***

The Role of Transgenic Rats in a Genome Wide Association Studies (GWAS) World

Howard Jacob, Medical College Wisconsin, Milwaukee, USA

Title(s): Professor, Department of Physiology and Pediatrics; Warren P. Knowles Chair of Genetics; Director of the Human and Molecular Genetics Center (Http://www.hmgc.mcw.edu); and Associate Section Chief of Genetics, Medical College of Wisconsin. Founder and member of the Board of Directors PhysioGenix, Inc.

(http://www.physiogenix.com).

Research Interests: Physiological genetics, renal physiology, genetic dissection of complex disease, disease interaction, integrative physiology, cardiovascular physiology, NextGen sequiencing.

Patents: Rat Model of Diabetic Nephropathy; Methods and Composition for Pharmacological and Toxicological Evaluation of Test Agents.

Education: BS, Biology, Iowa State University, 1983; PhD, Pharmacology, University of Iowa, 1989; Postdoctoral Fellow, Hypertension Training Program, Harvard Medical School, 1991; Postdoctoral Fellow, Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, 1992; Postdoctoral Fellow, Cardiology, Stanford University, 1992.

Honors: Merck, Sharpe and Dohme Travel Award for Outstanding Cardiovascular Research, 1991; Sokol Post Doctoral Fellowship Award, Whitehead Institute for Biomedical Research, 1991; Elected Fellow in the Council for High Blood Pressure, 1998; American Physiological Society, Bowditch Award and Lecturer (Young Investigator Award), 1999; Warren P. Knowles Chair of Genetics, 1999; 2007 A. Ross McIntyre Award, University of Nebraska.

6:00 – 6:15 pm

IG-CSG- cellular systems genomics
Stefan Wiemann

Stefan Wiemann (DKFZ Heidelberg, Germany)

Graduated from the biological faculty, University of Kaiserslautern and from German Cancer Research Center Heidelberg. He was visiting scientist at the European Molecular Biology Laboratory (EMBL) from 1992-1995, and then group leader in the division of Molecular Genome Analysis at the DKFZ. He was coordinator of the German cDNA Consortium and led research networks in DHGP and NGFN. He has been member of the faculty of biosciences of Heidelberg University since 2003. As of this year he is coordinator of the Integrated Network Cellular Systems Genomics in the Program for Medical Genome Research, and is acting head of the division Molecular Genome Analysis at DKFZ.

Current research:
Generation and application of genomics resources to analyze protein and miRNA activities in cancer-relevant processes. Systems biological modeling of signaling networks based on qualitative and quantitative genomic and proteomic data. In-vitro and in-vivo validation of findings aiming to improve cancer diagnosis and therapy.

Selected publications:
Sauermann et al., (2008) Reduced expression of vacuole membrane protein 1 affects the invasion capacity of tumor cells. *Oncogene*, 27:1320-6
Sahin et al., (2007) Combinatorial RNAi strategy: The next generation of quantitative protein network analysis. *Proc Natl Acad Sci U S A*, 104:6579-6584

6:15 – 6:30 pm

Identification of new targets playing a role in metabolic diseases by systemic analysis in the German Mouse Clinic
Jan Rozman

Until 1993 Jan Rozman studied biology at the University of Bielefeld and passed there his PhD in the field of avian energetics (thesis: Regulation of Body Mass and Reproduction in Australien Zebra Finches – Effects of photoperiod, temperature and diet) with a Fellowship by Studienstiftung des Deutschen Volkes. Between 1998 and 2001 he carried out his postdoctoral studies at the Department of Zoology at the "La Trobe University Melbourne/Australia) with a Fellowship by BASF AG and DFG. From 2001 to 2004 he worked as research staff in EU project "Quality of life and management of living resources" in a study on diet induced obesity in Sprague Dawley rats, Animal Physiology at the Philipps-Universität in Marburg. From 2004 to 2006 he was part of the research staff Animal Physiology at the Philipps-Universität of Marburg. Since 2006 Jan Rozmann is member of the research staff in NGFN project as well as Laboratory Manager of the Energy Metabolism Screen (1PhD, 1 technical assistant) in the Mouse Clinic, HMGU Munich (additional affiliation: Fachgebiet Molekulare Ernährungsmedizin, Zentralinstitut für Ernährungs- und Lebensmittelforschung, Wissenschaftszentrum Weihenstephan, TU München).

Research interests:
Regulation of energy balance in endotherm vertebrates, body mass regulation, body temperature regulation, obesity research in rodent models, imaging methods (DEXA, CT, MRT in mice)

6:30 – 6:45 pm

Modulation of neuropathic pain by endocannabinoids
Ildikó Rácz

From 1981to1986 Ildikó Rácz studied Natural Sciences at the Faculty of Natural Sciences, "Kossuth Lajos" University of Sciences, Debrecen and at "Eötvös Lóránd" University of Sciences, Budapest in Hungary. In 1986 she passed her M.S.C. in Biology and in 1996 her PhD degree at the Eötvös Lóránd University. Between 1986 and 1991 she was research fellow of the Department of Biology at the Alkaloida Chemical Factory, Tiszavasvári in Hungary and from 1991 to 1998 at the Experimental Research Laboratory, National Institute of Traumatology, Budapest in Hungary. She was Postdoctoral research fellow at the Laboratory of Molecular Neurobiology, University of Bonn from 2001 to 2006. Since then she is working as postdoctoral research fellow at the Institute of Molecular Psychatry, University of Bonn.

Research Interest: Animal models for addictive disorders, nociception phenotyping
Methods: behavioral analysis, microsurgery, pain-related studies, Neuropathic pain model

6:45 – 7:00 pm

Myosin light chain-1 controls cardiac contractility
Benjamin Meder

He studied medicine from 1998 to 2005 at the Albert-Ludwigs-University in Freiburg and passed his Doctoral Thesis in 2004.

He received an E-fellows scholarship (Munich) from 2001 to 2005 (Munich) and from Bayer AG (Leverkusen) from 2003 to 2005.
Between 2005 and 2008 he worked as Physician at the University Hospital of Heidelberg.
Since 2005 until present Benjamin Meder is postdoctoral research fellow of the group of PD Dr.med. Wolfgang Rottbauer (NGFN Funding) at the University of Heidelberg and since 2008 Head of the Laboratory of Molecular Genetics (NGFN Funding) for the Department of Internal Medicine III at the University Hospital of Heidelberg
Research Activities:
Molecular Cardiology: Zebrafish as model-organism for genetic cardiomyopathies
Etiology and pathogenesis of cardiomyopathies
Genetics of human cardiomyopathies – mutation screening
Clinical Cardiology: Clinical features of cardiomyopathies
New therapeutic approaches for cardiomyopathies
Memberships: Deutsche Gesellschaft für Kardiologie

Evening Lecture:

7:00 – 8:00 pm

High resolution proteomics in functional genomics
Matthias Mann

Matthias Mann, Professor, PhD. received his doctorate degree from Yale University in 1988. After a postdoctoral stay with Prof. Peter Roepstorff at University of Southern Denmark in Odense, he 1992-1998 joined the European Molecular Biology Laboratory (EMBL) as group leader. 1998-2007 he was Professor in Bioinformatics, University of Southern Denmark.

Since 2005 he is as well Director at the Max Planck Institute of Biochemistry in Munich, Germany.
In 2007 Dr. Mann furthermore was appointed as Honorary Professor and head of Department of Proteomics at the newly founded Novo Nordisk Foundation Center for Protein Research at University of Copenhagen, Denmark.
Dr. Mann, who is among the most highly cited researchers in Europe, has been elected to membership of the European Molecular Biology Organization as well as the Royal Danish Academy of Arts and Sciences and also to a visiting professorship at Harvard Medical School.

8:00 pm - open end: ***Get-Together & Dinner***

Saturday, December 13th, 2008

Symposium V: Genomic / Environmental Interaction

(Chairs: Markus Nöthen, H.-Erich Wichmann)

9:00 – 9:45 am

Opening Keynote Presentation

From genome wide association studies to risk prediction: the importance of studies of gene interactions
Cornelia M. van Duijn

CM van Duijn, PhD. Dr van Duijn is a professor of Genetic Epidemiology at the Department of Epidemiology & Biostatistics, Erasmus University Medical School Rotterdam, The Netherlands. She has been involved in genetic-epidemiological studies of various complex disorders including Alzheimer's disease, Parkinson's disease, Creutzfeldt-Jakob disease, stroke, diabetes, osteoarthritis and osteoporosis. She is one of the principle investigators of the Rotterdam study, a population-based study of 12,000 subjects age 55 years and older who have been followed over 10 years, where she is responsible for the bio-bank and statistical genetic analysis. Together with Prof Dr BA Oostra she heads the Genetic Research in Isolated Populations (GRIP) program, a research program in a genetically isolated population in the South Western part of the Netherlands, which includes the Erasmus Rucphen Family (ERF) study of 2500 relatives from the GRIP region who go back to 30 closely related (first and second degree) founding couples living in the isolate in the period 1850-1900. Within the Netherlands, Dr van Duijn is the coordinator of the platform Epidemiology of the Center for Medical Systems Biology (CMSB), one of the centres of excellence of the Dutch Genomics initiative. She is further the program director of the genetic-epidemiology teaching program of the Netherlands Institute for Health Sciences (nihes).

9:45 – 10:00 am

Genetics meets metabolomics: a genome-wide association study of metabolite profiles in human serum
Christian Gieger

Christian Gieger studied Mathematics at the Technische Universität München from 1986 -1987 and continued with Statistics from 1987 to 1993 at the Ludwig-Maximilians-Universität München where he passed his PhD in 1998 as well. Between 1993 and 1998 he worked as research associate, Chair of Statistics and its Applications under Prof. Dr. Ludwig Fahrmeir, Institute for Statistics at the University of Munich and between 1995 and 1999 at the Collaborative Research Center SFB 386.

From 1999 to 2000 he was IT architect in the Center for e-Business at IBM Heidelberg.
Between 2000 and 2002 he worked as Senior Scientist at the Department of Life Science Informatics Research, LION bioscience AG, Heidelberg and from 2002 to 2004 as Senior Scientist at the Fraunhofer Institute for Algorithms and Scientific Computing (SCAI), Sankt Augustin.
Since 2004 he is Senior Scientist and project leader at KORA-gen at the Institute of Epidemiology of the Helmholtz Zentrum München and worked additionally until 2008 as well at the Chair of Epidemiology, IBE, Ludwig-Maximilians-Universität München.

SCIENTIFIC INTERESTS

Genome-wide association studies
Genetic epidemiology of complex diseases
Statistical analysis of genetic and molecular data
Genetics of metabolic profiles (metabolomics)
Biobanking and biological databases

10:00 – 10:15 am

Response to ultrafine particle instillation in two mouse strains with extremely divergent lung function
Tobias Stoeger

Dr. Stoeger is a molecular biologist heading the "particle health effects" group at the HMGU Institute of Inhalation Biology. His research interests range from acute effects caused by the inhalation of nanoparticles to their use for therapeutic applications. Current main research topics of his group are: mechanisms of acute effects caused by particle/cell interactions, relationships between physical-chemical particle characteristics and their toxicity, and genetic susceptibility for particle health effects. Methods of investigation focus on tissue culture models and controlled animal exposures, with special emphasis on genetic modified mouse strains. Dr. Stoeger received his diploma in biology and his Ph.D. from the Technical University Munich, in developmental biology and mouse genetics in the research lab of Prof. Dr. R. Balling. After working 4 years for the pharmaceutical industry, by developing mouse models for drug targeting, he joined the HMGU Institute of Inhalation Biology five years ago.

10:15 – 10:30 am

Alcoholism – A Systems approach from molecular physiology to addictive behaviour
Rainer Spanagel

He studied biology at the University of Tübingen and at the Technical University of Munich and passed his diploma in 1989. Rainer Spanagel received his doctorate degree in 1991 working under Prof. Albert Hertz of the Max Planck Institute of Neuropharmacology in Martinsried, Germany.

From 1991 to 1995 he was first working as scientific assistant at the Max Planck Institute of Psychiatry in Munich in the department of Prof. Florian Holsboer and became then Head of the research groupe "Drug Addiction" from 1996 to 1999. In 1997 he worked additionally for the University of Munich at the Habilitation in Pharmacology & Toxicology department under Prof. Wolfgang Forth.
In 1999 he became Professor for Psychopharmacology at the University of Heidelberg and the Central Institute of Mental Health (CIMH) in Mannheim, Germany
Since 2000 he is Department head of Psychopharmacology at the Central Institute of Mental Health (CIMH)
Awards: INVEST NIDA Award 1995
Wilhelm Feuerlein Award for Alcohol Research 1998
Sir Hans Krebs Award 2003
Albrecht-Ludwig-Berblinger Award 2005
James B. Isaacson Award 2008

10:30 – 10:45 am

Tbc1d1 mutation confers leanness and protects from diet-induced obesity and diabetes
Hadi Al-Hasani

Dr. Al-Hasani's research is focused on insulin action in adipose cells and skeletal muscle, and the identification of disease candidate genes for obesity and type-2 diabetes in polygenic mouse models. He has studied Biology and earned his Ph.D. in Biochemistry from the University of Cologne. After three years postdoctoral work (1996-1998) as a DFG-fellow in Dr. Samuel W. Cushman's laboratory at the Diabetes Branch, NIDDK at the National Institutes of Health in Bethesda, MD, USA, where he received the NIH fellows award for research excellence, he returned with a grant from the Federal Ministry of Education and Research (BMBF) to the Center for Molecular Medicine at the Medical Faculty, University of Cologne to continue research on insulin action. In 2002, he received his Habilitation in Biochemistry from the University of Cologne and joined Prof. Dr. Dr. Hans-Georg Joost as group leader at the German Institute for Human Nutrition (DIfE) in Potsdam.

10:45 – 12:45 pm

Lunch Break and Poster Session II – Posters Symposia V-VI

10:45 – 12:45 pm **Company Satellite Lunch Sessions**

Roche Diagnostics GmbH
LightCycler 480 System (Real-Time PCR)

Illumina Ltd
Genotyping and Gene-expression updates from Illumina

TMF e.V.
Contact partner and common platform for networked medical research

Symposium VI: Transfer from Genomics to Application

(Chairs: Markus Hecker, Birte Sönnichsen)

12:45 – 1:30 pm ***Opening Keynote Presentation***

From Genomes to Drugs
Bert Klebl

Bert Klebl gathered more than 10 years of professional experience in drug discovery and early drug development from various positions in the life-science industry, finally as Senior Director Discovery Biology and Head of Biology at GPC Biotech. Before that he was Axxima's Vice President Research responsible for discovery and development of the company's portfolio of kinase inhibitors for various therapeutic indications. In previous positions he worked as project team leader and senior scientist with Aventis and Hoechst Marion Roussel. A biochemist by training he earned his Ph.D. in Biochemistry at the University of Konstanz, Germany and did post-doctoral work at the Biotechnology Research Institute of the NRC Canada in Montréal, Canada. In the course of his research work he published more than 30 articles in peer-reviewed journals and is a co-inventor of more than 15 patent and patent applications.

1:30 – 1:45 pm ***Defining PI3-Kinase dependency in non-small cell lung cancer***
Martin Sos

Graduated from Medical School, University of Cologne, 2007

Graduate student 2006-2007, Köln Fortune fellowship holder

Graduate student fellowship award (DGHO 2008)

Post-doc in the Max-Planck-Institute for Neurological Research in the group of Adjunct Professor Dr. Roman Thomas. Main focus: genome wide lesion analysis, cell signalling, high-throughput cellular screening.

1:45 – 2:00 pm

Functional impact of polymorphisms on the human delta-6 desaturase gene promoter
Eva Lattka

Since April 2007 Eva Lattka is PhD student at the Helmholtz Zentrum München, Institute of Epidemiology, Unit Biological Samples-Genomics. From October 2006 to March 2007 she already worked as Scientific Assistant at the Helmholtz Zentrum München, Institute of Experimental Genetics, Unit Molecular Endocrinology. Between 2001 and 2006 she studied Biochemistry at the Technical University Munich and passed her Master of Science in Biochemistry in August 2006.

2:00 – 2:15 pm

Xenogeneic immunization with human tyrosine hydroxylase DNA vaccines effectively eradicates established neuroblastoma and induces long lasting protective immunity
Nicole Huebener

After finishing high school in 1995, Nicole Huebener started her studies in biology at the Martin-Luther-University Halle-Wittenberg. In October 2000 she finished the studies with her diploma thesis at the Institute of Microbiology under the supervision of Prof. Dietrich H. Nies, therein summarizing her scientific work about the chromate resistance of the chemolithoautotrophic bacterium Ralstonia metallidurans CH34.

Dr. Huebener's scientific work changed towards translational research when she started her work as a PhD student in the Experimental Oncology group of Prof. Holger N. Lode in March 2001 at the Charité-Universitätsmedizin Berlin. She finished her PhD in Immunology at the Humboldt University Berlin in March 2007 with the defense of her thesis "Vaccination with murine tyrosine hydroxylase DNA vaccines for anti-neuroblastoma immunotherapy". Since then she works in Holger Lode's group as a PhD, evaluating new immunotherapeutic strategies for the challenging childhood tumor neuroblastoma.

2:15 – 2:30 pm

High-throughput sequencing of snap frozen and paraffin embedded cancer and normal tissues
Michal-Ruth Schweiger

MICHAL-RUTH SCHWEIGER as a fellow of the 'Studienstiftung des Deutschen Volkes' received her M.D. in 2001 with a *summa cum laude* (Dr. med.). In parallel to Medicine she studied Biochemistry, received her diploma in 2002 and graduated with a Ph.D. *summa cum laude* (Dr.rer.nat) from the Free University of Berlin in 2005. For her work on Papillomaviruses she received the Robert Koch Dissertation award from the Charité. For her graduate and post-graduate work she joined for four years Prof.P.M.Howley's group at the Harvard Medical School in Boston. She then returned to Germany and is currently working as a group leader in Prof.H.Lehrach's department at the MPI in Berlin. Her previous and current scientific work focuses on protein kinase C (PKC) signalling, the mechanism of infection of Papilloma viruses, the pathogenesis of cancer and the development of high throughput sequencing techniques for cancer diagnosis.

2:30 – 2:45 pm	***Technology transfer in the program for medical genome research*** **Isabel von Korff**
2:45 – 3:00 pm	**Ceremony: "Annemarie Poustka Poster Award of Medical Genome Research" sponsored by Roche Diagnostics GmbH**
	Concluding Remarks: Hugo Katus, Speaker Project Committee of NGFN-Plus / NGFN-Transfer in the Program of Medical Genome Research

National Genome Research Network

Overviews

National Genome Research Network

Oral Presentations

Page	Abstract	Submitting Author	Abstract Title	Consortium
			Symposium I – Genomics of Common Disease	
77	O-1-1	Samani, Nilesh	*Genetics of CAD (coronary artery disease): an update*	
78	O-1-2	Pfeufer, Arne	*Common variants at ten loci modulate the QT interval duration in individuals of European ancestry: the QTSCD consortium*	*IG Genetics of Heart Failure*
79	O-1-3	Rietschel, Marcella	*Genome-wide association study of alcohol dependence*	*IG Genetics of Alcohol Addiction*
80	O-1-4	Cichon, Sven	*Large recurrent microdeletions associated with schizophrenia*	*IG Molecular Causes of Major Mood Disorders and Schizophrenia (MooDS)*
82	O-1-5	Heid, Iris	*Meta-analyses of genome-wide association studies: six new obesity associated loci highlight a neuronal influence on body weight regulation*	*IG-Adipositas*
83	O-1-6	Franke, André	*Genome-wide scan reveals association of psoriasis with IL-23 and NF-kB pathways*	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
84	O-1-7	Illig, Thomas	*Genome-wide scan on total serum IgE levels identifies FCER1A as novel susceptibility locus*	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
			Symposium II – Systems Biology	
89	O-2-1	Herwig, Ralf	*Integration of human molecular interactions*	*IG Systems Biology of Genetic Diseases (Mutanom)*
90	O-2-2	Arunachalam, Vinayagam	*Constructing a causal protein interaction network for activated MAPK signalling*	*IG Neurodegenerative Diseases Networks (NeuroNet)*
91	O-2-3	Dölken, Lars	*High resolution gene expression profiling for simultaneous kinetic parameter analysis of RNA synthesis and decay*	*IG Pathogenic Role of mi-RNA in Herpes-Infections*
92	O-2-4	Johannes, Marc	*Predicting pathway membership via domain signatures*	*IG Prostate Cancer*
			Symposium III – Genome Regulation	
95	O-3-1	Vingron, Martin	*Computational Regulatory* Genomics	
96	O-3-2	Selbach, Matthias	*Genome-wide identification of microRNA targets by pulsed stable isotope labelling (pSILAC)*	*IG Neurodegenerative Diseases Networks (NeuroNet)*
97	O-3-3	Hoheisel, Jörg	*Looking at microRNA and mRNA profiles and related epigenetic variations in promoter regions of pancreatic cancer samples*	*IG Genome Research Network in Pancreatic Cancer*
98	O-3-4	Schulte, Johannes	*Histone demethylase LSD1 is highly expressed in poorly differentiated neuro-blastoma and is a novel therapeutic target*	*IG Neuroblastoma Genome Interaction Network*

Page	Abstract	Submitting Author	Abstract Title	Consortium
99	O-3-5	Supper, Jochen	*Predicting DNA-binding specificities of transcription factors*	*IG Functional Genomics of Parkinson*
			Symposium IV – Animal, Cellular & Tissue Models	
103	O-4-1	Jacob, Howard	*The Role of Transgenic Rats in a Genome Wide Association Studies (GWAS) World*	
104	O-4-2	Wiemann, Stefan	*IG-CSG- cellular systems genomics*	*IG Cellular Systems Genomics in Health and Disease*
105	O-4-3	Rozmann, Jan	*Identification of new targets playing a role in metabolic diseases by systemic analysis in the German Mouse Clinic*	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
106	O-4-4	Ildikó Rácz	*Modulation of neuropathic pain by endocannabinoids*	*IG Neurodegenerative Diseases Networks (NeuroNet)*
107	O-4-5	Meder, Benjamin	*Myosin light chain-1 controls cardiac contractility*	*IG Genetics of Heart Failure*
			Symposium V – Genomic / Environmental Interaction	
111	O-5-1	Van Duijn, Cornelia	*From genome wide association studies to risk prediction: the importance of studies of gene interactions*	
112	O-5-2	Gieger, Christian	*Genetics meets metabolomics: a genome-wide association study of metabolite profiles in human serum*	*NGFN2*
113	O-5-3	Stoeger, Tobias	*Response to ultrafine particle instillation in two mouse strains with extremely divergent lung function*	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
114	*O-5-4*	Spanagel, Rainer	*Alcoholism – A Systems approach from molecular physiology to addictive behaviour*	IG Genetics of Alcohol Addiction
115	*O-5-5*	Al-Hasani, Hadi	*Tbc1d1 mutation confers leanness and protects from diet-induced obesity and diabetes*	*IG Molecular Mechanisms in Obesity*
			Symposium VI – Transfer from Genomics to Application	
119	O-6-1	Klebl, Bert	*From genomes to drugs*	
120	O-6-2		*Defining PI3-Kinase dependency in non-small cell lung cancer*	*IG Deciphering Oncogene Dependencies*
121	O-6-3	Lattka, Eva	*Functional impact of polymorphisms on the human delta-6 desaturase gene promoter*	*IG Molecular Mechanisms in Obesity*
122	O-6-4	Huebener, Nicole	*Xenogeneic immunization with human tyrosine hydroxylase DNA vaccines effectively eradicates established neuroblastoma and induces long lasting protective immunity*	*IG Neuroblastoma Genome Interaction Network*

Page	Abstract	Submitting Author	Abstract Title	Consortium
123	O-6-5	Schweiger, Michal-Ruth	*High-throughput sequencing of snap frozen and paraffin embedded cancer and normal tissues*	*IG Modifiers of Intestinal Tumor Formation and Progression*
			Evening Lecture	
124	Evening Lecture	Mann, Matthias	*High resolution proteomics in functional genomics*	

National Genome Research Network

List of poster abstracts

sorted by Symposia

All posters will be displayed continuously throughout the duration of the meeting. Authors will be present at their posters for discussion during the designated time of their respective poster session.

Poster Session I: Posters Symposia I-IV
Friday, December 12th 2008
1:00 – 3:00 pm

Poster Session II: Posters Symposia V-VI
Saturday, December 13th 2008
10:45 – 12:45 pm

Page	Abstract	Submitting Author	Abstract Title	Consortium
			Symposium I – Genomics of Common Disease	
131	P-1-1	Radlwimmer, Bernhard	Global analyses of molecular differentiation pathways in brain-tumor stem cells	*IG Brain Tumor Network*
132	P-1-2	Sahin, Özgur	Identification of oncomirs targeting feedback regulators of EGFR signaling	*IG Cellular Systems Genomics in Health and Disease*
133	P-1-3	Tschulena, Ulrich	A novel large-scale screen to identify modulators of miR-21	*IG Cellular Systems Genomics in Health and Disease*
134	P-1-4	Sauter, Wiebke	Case-control study of genetic susceptibility in early onset lung cancer: Investigation of *Matrix Metalloproteinase 1* (*MMP1*)	*IG Deciphering Oncogene Dependencies*
135	P-1-5	Todt, Unda	New genetic evidence for involvement of the dopamine system in migraine with aura	*IG Epilepsy and Migraine Integrated Network (EMINet)*
136	P-1-6	Maljevic, Snezana	A trafficking defective $K_V7.2$ mutation causing neonatal seizures	*IG Epilepsy and Migraine Integrated Network (EMINet)*
137	P-1-7	Wurst, Wolfgang	From Disease Genes to Protein Pathways: the DIGTOP project	*IG From Disease Genes to Protein Pathways (DiGTOP)*
138	P-1-8	Büchel, Finja	ProDGe - a sequence and protein interaction viewer	*IG Functional Genomics of Parkinson*
139	P-1-9	Gloeckner, Christian	The Parkinson disease-associated protein kinase LRRK2 shares sequence homology with MAP3K and phosphorylates classical MAP3K targets, *in vitro*	*IG Functional Genomics of Parkinson*
140	P-1-10	Sharma, Manu	Genome-wide association study in Parkinson's disease reveals strong association signals in the SNCA AND MAPT genes	*IG Functional Genomics of Parkinson*
141	P-1-11	Elstner, Matthias	Gene expression analysis in dopaminergic neurons of the substantia nigra reveals candidate genes and differentially regulated pathways in Parkinson disease	*IG Functional Genomics of Parkinson*
142	P-1-12	Nitz, Barbara	Genome wide association study and analysis of candidate genes on nicotine dependence	*IG Genetics of Alcohol Addiction*
143	P-1-13	Drews, Eva	QTL analysis of endophenotypes related to alcoholism	*IG Genetics of Alcohol Addiction*
144	P-1-14	Malzahn, Dörthe	Longitudinal gene-gene and gene-time effects on body mass index for variants near *INSIG2* and in the *MC4R* gene	*IG Genetics of Heart Failure*
145	P-1-15	Schulz, Angela	Conversion of the salt-resistant phenotype of spontaneously hypertensive rats into a salt-sensitive phenotype leads to severe cardiac hypertrophy in a new double-consomic rat model	*IG Genetics of Heart Failure*
146	P-1-16	Katus, Hugo	Chromosome 9q21 as a new major susceptibility locus for dilated cardiomyopathy	*IG Genetics of Heart Failure*
147	P-1-17	Preuss, Christoph	Evolutionary dynamics of gene cluster rearrangements associated with complex diseases	*IG Genetics of Heart Failure*

Page	Abstract	Submitting Author	Abstract Title	Consortium
148	P-1-18	Knöll, Ralph	Novel Z-disk proteins and cardiac-mechanosensation	*IG Genetics of Heart Failure*
149	P-1-19	Gieger, Christian	A genome wide association study reveals SLC2A9 as a major gene for uric acid levels with pronounced sex-specific effects	*NGFN-2*
150	P-1-20	Bisping, Egbert	Applicability and relationship of E/e', LAVI, age, natriuretic peptides and hypertrophic markers in diastolic dysfunction and diastolic heart failure	*IG Genetics of Heart Failure*
151	P-1-21	Bisping, Egbert	Genome-wide association analysis of left ventricular hypertrophy and diastolic heart failure	*IG Genetics of Heart Failure*
152	P-1-22	Erdmann, Jeanette	Novel susceptibility locus for coronary artery disease on chromosome 3q22.3	*IG Genomics of Atherosclerosis*
153	P-1-23	Eifert, Sandra	Systematic pathway-analysis of Kinesin Protein Family (KIF) using genome-wide SNP data in patients with myocardial infarction: Genetic variation in KIF17 gene associates with myocardial infarction	*IG Genomics of Atherosclerosis*
154	P-1-24	Eifert, Sandra	First genome-wide association study in patients underwent Coronary Artery Bypass Grafting (CABG) under gender specific perspectives	*IG Genomics of Atherosclerosis*
155	P-1-25	Koenig, Wolfgang	No association between monocyte chemoattractant protein-1 (MCP-1) gene polymorphisms and incident type 2 diabetes mellitus (T2DM) in middle-aged men and women: results from the MONICA/KORA Augsburg case-cohort study, 1984-2002	*IG Genomics of Atherosclerosis*
156	P-1-26	Koenig, Wolfgang	Monocyte chemoattractant protein-1 (MCP-1) gene polymorphisms, MCP-1 plasma levels and incident coronary heart disease (CHD) in middle-aged men and women: Results from the MONICA/KORA Augsburg case-cohort study, 1984-2002	*IG Genomics of Atherosclerosis*
157	P-1-27	Khuseyinova, Natalie	No association between C-reactive Protein (CRP) gene polymorphisms, CRP haplotypes and incident type 2 diabetes mellitus (T2DM) in middle-aged men and women: results from the MONICA/KORA Augsburg case-cohort study, 1984-2002	*IG Genomics of Atherosclerosis*
158	P-1-28	Medack, Anja	Comperative mapping of linkage and association results in myocardial infarction	*IG Genomics of Atherosclerosis*
159	P-1-29	Zeller, Tanja	From genomics to transcriptomics - genome-wide association - and expressionanalyses in the population-based Gutenberg Heart Study	*IG Genomics of Atherosclerosis*
160	P-1-30	Müller, Martina	A genome-wide association analysis of HDL-cholesterol in the population-based KORA study sheds new light on intergenic regions	*IG Genomics of Atherosclerosis*
161	P-1-31	Aherrahrou, Zouhair	No association between the connexin37 gene polymorphism C1019T and myocardial infarction in a German population	*IG Genomics of Atherosclerosis*

Page	Abstract	Submitting Author	Abstract Title	Consortium
162	P-1-32	Aherrahrou, Zouhair	Association of SNP rs671699 in the connexion 37 gene with coronary artery calcification	*IG Genomics of Atherosclerosis*
163	P-1-33	Eck, Sebastian	Analysis of copy number variation in a population based study using high density SNP microarrays	*IG German Mental Retardation Network (MRNET)*
164	P-1-34	Butuzova, Kateryna	Characterisation of a new ENU induced mouse model for Polycytemia Vera	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
165	P-1-35	Mannsperger, Heiko	Large Scale Quantitative Analysis of Tumor Samples using Protein Microarrays	*IG Integrated Genome Network of Prostate Cancer*
166	P-1-36	Ummanni, Ramesh	Identification and characterization of new clinically applicable target proteins in prostate cancer	*IG Integrated Genome Network of Prostate Cancer*
167	P-1-37	Brase, Jan Christoph	Antibody-based signal amplification improves specific target detection on reverse phase protein arrays	*IG Integrated Genome Network of Prostate Cancer*
168	P-1-38	Minner, Sarah	Low level HER2 overexpression is associated with rapid tumor cell proliferation and poor prognosis in prostate cancer	*IG Integrated Genome Network of Prostate Cancer*
169	P-1-39	El Gammal, Alexander	Chromosome 8p deletions and 8q gains are associated with tumor progression and poor prognosis in prostate cancer	*IG Integrated Genome Network of Prostate Cancer*
170	P-1-40	Lascorz, Jesus	Genome-wide association study for colorectal cancer in German familial cases and replication in independent cohorts	*IG Integrated Genomic Investigation of Colorectal Carcinoma*
171	P-1-41	Boutros, Michael	Systematic dissection of Wnt signaling networks	*IG Integrated Genomic Investigation of Colorectal Carcinoma*
172	P-1-42	Hoehe, Margret	NGFN-Plus IG: MHC haplotype sequencing: An integrated approach to common disease	*IG MHC Haplotype Sequencing: An Intergrated Approach to Common Disease*
173	P-1-43	Morkel, Markus	Identification of modifiers of intestinal tumor formation and progression using mouse B6/PWD chromosome substitution strains	*IG Modifiers of Intestinal Tumor Formation and Progression*
174	P-1-44	Lucae, Susanne	A genome-wide association study in major depression reveals association of SNPs on chromosome 12q21.31	*IG Molecular Causes of Major Mood Disorders and Schizophrenia (MooDS)*
175	P-1-45	Kloiber, Stefan	Variations in Tryptophan Hydroxylase 2 leading to decreased serotonergic activity are associated with elevated risk for metabolic syndrome in depression	*IG Molecular Causes of Major Mood Disorders and Schizophrenia (MooDS)*
176	P-1-46	Barth, Alexander	Identification of QTLs influencing anxiety and depression in mice	*IG Molecular Causes of Major Mood Disorders and Schizophrenia (MooDS)*

Page	Abstract	Submitting Author	Abstract Title	Consortium
177	P-1-47	Emeny, Rebecca	Single nucleotide polymorphism associations with Type-D personality in the general population; findings from the KORA K-500-substudy	*IG Molecular Causes of Major Mood Disorders and Schizophrenia (MooDS)*
178	P-1-48	Mössner, Rainald	Systematic investigation of the molecular causes of major mood disorders and schizophrenia (MooDS): SP3: Genomics of Schizophrenia	*IG Molecular Causes of Major Mood Disorders and Schizophrenia (MooDS)*
179	P-1-49	Bettecken, Thomas	No evidence for DUP25 in anxiety patients, as judged by molecular karyotyping	*IG Molecular Causes of Major Mood Disorders and Schizophrenia (MooDS)*
180	P-1-50	Rößler, Paula	Gene-Gene interaction between *APOA5* and *USF1*: Two candidate genes for the metabolic syndrome	*IG Molecular Mechanisms in Obesity*
181	P-1-51	Hinney, Anke	Gastric inhibitory polypeptide receptor: Association analyses of several polymorphisms in large study groups pertaining to obesity	*IG Molecular Mechanisms in Obesity*
182	P-1-52	Grallert, Harald	Genetic variation in the *Resistin* locus and components of the metabolic syndrome in 5100 subjects	*IG Molecular Mechanisms in Obesity*
183	P-1-53	Schäfer, Helmut	Planning genome wide association studies under limited budget	*IG Molecular Mechanisms in Obesity*
184	P-1-54	Hinney, Anke	Large family-based genome-wide association scan for early onset extreme obesity	*IG Molecular Mechanisms in Obesity*
185	P-1-55	Bolze, Florian	The premature nonsense mutation W16X in the melanocortin-4-receptor gene causes obesity in mice	*IG Molecular Mechanisms in Obesity*
186	P-1-56	Friedel, Susann	NGFN^{PLUS}-Network "molecular mechanisms in obesity"	*IG Molecular Mechanisms in Obesity*
187	P-1-57	Grothe, Jessica	Obesity relevant melanocortin-4-receptor gene variants and identity by descent: Analysis of single nucleotide polymorphisms - not only in the context of association studies	*IG Molecular Mechanisms in Obesity*
188	P-1-58	Scherag, André	Novel genetic variants for obesity identified in a joint analysis of two genome-wide association scans for early onset extreme	*IG Molecular Mechanisms in Obesity*
189	P-1-59	Poschmann, Gereon	Proteomic profiling of mouse hypothalamus in strains susceptible or resistant to diet-induced obesity	*IG Molecular Mechanisms in Obesity*
190	P-1-60	Vogel, Heike	*Nob3* - A major QTL for obesity on mouse chromosome 1	*IG Molecular Mechanisms in Obesity*
191	P-1-61	Fisher, Eva	The fat-mass and obesity associated *(FTO)* rs9939609 single nucleotide polymorphism is associated with high C-reactive protein levels independently from obesity indices in EPIC-Potsdam	*IG Molecular Mechanisms in Obesity*
192	P-1-62	Schulte, Johannes	MicroRNAs in the pathogenesis of neuroblastoma	*IG Neuroblastoma Genome Interaction Network*

Page	Abstract	Submitting Author	Abstract Title	Consortium
193	P-1-63	Lohmann, Katja	Heterozygous *ATP13A2* variants in patients with early-onset Parkinson disease and controls	*IG Neurodegenerative Diseases Networks (NeuroNet)*
194	P-1-64	Dittmer, Alexandra	Interactions of viral and cellular miRNAs in the MCMV system	*IG Pathogenic Role of mi-RNA in Herpes-Infections*
195	P-1-65	Kuner, Ruprecht	Sample preparation for an integrated analysis of genomic, transcriptomic, and proteomic markers from the same tissue source	*IG Prostate Cancer Network*
196	P-1-66	Schreiber, Stefan	Systematic full resequencing of patient populations to assess genetic susceptibility in complex diseases	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
197	P-1-67	Flachsbart, Friederike	Systematic detection of genetic variation associated with exceptional life expectancy in humans	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
198	P-1-68	Rodriguez, Elke	Analysis of gene-gene interaction within the filaggrin pathway	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
199	P-1-70	Huse, Klaus	Clinical impact of defensin copy number variation	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
200	P-1-71	Nothnagel, Michael	A comprehensive evaluation of SNP genotype imputation	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
201	P-1-72	Suttner, Kathrin	Genetic variants in the transcription factors T-bet, HLX1 and GATA3 and their functional role in the development of asthma	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
202	P-1-73	Esparza Gordillo, Jorge	Genome-wide association study for atopic dermatitis	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
203	P-1-74	Hofmann, Sylvia	Identification of *ANXA11* as a novel risk locus for saroidosis by a genomewide association study	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
204	P-1-75	Schedel, Michaela	Allele-specific NF-kB-binding alters STAT6 expression and contributes to genetic IgE control	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
205	P-1-76	Franke, André	Sequence variants in IL10, ARPC2 and multiple other loci contribute to ulcerative colitis susceptibility	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
206	P-1-77	Weber, Yvonne	A GLUT1 mutation in patients with constant spastic paraplegia and	*IG Systems Biology of Genetic Diseases*

Page	Abstract	Submitting Author	Abstract Title	Consortium
			paroxysmal dyskinesia	*(Mutanom)*
207	P-1-78	Lehrach, Hans	The German participation in the 1000 Genomes Project	*IG Systems Biology of Genetic Diseases (Mutanom)*
208	P-1-79	End, Caroline	Analysis of innate defence factors in esophageal and gastric cancer	*IG Systems Biology of Genetic Diseases (Mutanom)*
			Symposium II – Systems Biology	
213	P-2-1	Hosp, Fabian	Identification and quantification of protein-protein interactions in neurodegenerative diseases using mass spectrometry	*IG Neurodegenerative Diseases Networks (NeuroNet)*
214	P-2-2	Wanker, Erich	Detecting novel connections between neurodegenerative diseases: the NGFN-Plus consortium IG NeuroNet	*IG Neurodegenerative Diseases Networks (NeuroNet)*
215	P-2-3	Boutros, Michael	Large-scale rna interference screens and high-content analysis to dissect cellular pathways	*IG Neurodegenerative Diseases Networks (NeuroNet)*
216	P-2-4	Filiou, Michaela	Biomarker discovery via stable isotope metabolic labeling of a trait anxiety mouse model	*IG Systems Biology of Genetic Diseases (Mutanom)*
217	P-2-5	Lange, Bodo	IG mutanom - systems biology of genetic diseases	*IG Systems Biology of Genetic Diseases (Mutanom)*
218	P-2-6	Riechers, Sean-Patrick	Generation and systematic analysis of protein-protein interaction networks for cytoplasmic protein-tyrosine kinases in human cancer	*IG Systems Biology of Genetic Diseases (Mutanom)*
219	P-2-7	Horsch, Marion	Systematic gene expression profiling of a series of mouse models reveals co-expressed genes	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
220	P-2-8	Korf, Ulrike	Protein microarrays as tool for cancer systems biology	*IG Cellular Systems Genomics in Health and Disease*
221	P-2-9	Sahin,Özgür	Modeling ERBB receptor-regulated G1/S transition to find novel targets for de novo trastuzumab resistance	*IG Cellular Systems Genomics in Health and Disease*
222	P-2-10	Henjes, Frauke	Quantitative proteomics of growth factor receptor and hormone receptor signaling	*IG Cellular Systems Genomics in Health and Disease*
223	P-2-11	Adler, Thure	Immuno-phenotyping at the German Mouse Clinic. The clustering of T cell subsets.	*IG Cellular Systems Genomics in Health and Disease*
224	P-2-12	Hiersche, Milan	Analysis of genetic factors in disease susceptibility: An integrative systems biology concept	*IG Genomics of Atherosclerosis*
225	P-2-13	Dräger, Andreas	SBML2LaTeX: Conversion of SBML files into human-readable reports	*IG Functional Genomics of Parkinson*
226	P-2-14	Dräger, Andreas	Modeling metabolic networks: a comparison of rate laws in combination with various parameter optimization strategies	*IG Functional Genomics of Parkinson*
227	P-2-15	Dräger, Andreas	SBMLsqueezer: a CellDesigner plug-in to generate kinetic rate equations for biochemical networks	*IG Functional Genomics of Parkinson*
228	P-2-16	Schubert, Walter	Human TOPONOME project: Progress report	*IG Neuroblastoma Genome Interaction Network*

Page	Abstract	Submitting Author	Abstract Title	Consortium
229	P-2-17	Lawerenz, Chris	iCHIP- sustainable data pool services for Neuroblastoma	*IG Neuroblastoma Genome Interaction Network*
230	P-2-18	Fontaine, Jean Fred	Ranking the biomedical literature for optimised experimental designs	*IG Neurodegenerative Diseases Networks (NeuroNet)*
			Symposium III – Genome Regulation	
235	P-3-1	Sauer, Sascha	Modulating the action of nuclear receptors by natural products	*IG Molecular Mechanisms in Obesity*
236	P-3-2	Becker, Albert	Transcriptional key mechanisms in epilepsy: Induction of T-type calcium channel $Ca_V3.2$ expression by zinc	*IG Epilepsy and Migraine Integrated Network (EMINet)*
237	P-3-3	Kiełbasa, Szymon	Conservation of transcriptional autoregulatory feedback loop in vertebrates	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
238	P-3-4	Manke, Thomas	Quantitative models and prediction of regulatory interactions	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
239	P-3-5	Muro, Enrique	Pseudogenes as a source of trans-NAT seeds	*IG Neurodegenerative Diseases Networks (NeuroNet)*
240	P-3-6	Tschulena, Ulrich	A genome-wide RNAi screen to identify modulators of human P38 signalling	*IG Cellular Systems Genomics in Health and Disease*
241	P-3-7	Malterer, Georg	Identification of targets for KSHV-encoded miRNAs	*IG Pathogenic Role of mi-RNA in Herpes-Infections*
242	P-3-8	Anastasov, Natasa	NPM-ALK kinase activity influences miRNA expression in ALK+ Anaplastic Large Cell Lymphoma (ALCL)	
243	P-3-9	Weiler, Markus	The role of hypoxia-induced N-myc down-regulated gene 1 (NDRG1) in glioma biology	*IG Brain Tumor Network*
244	P-3-10	Rivera Brugués, Núria	Identification of disease-related copy number variation (CNV) in patients with mental retardation by high-dense SNP genotyping microarrays	*IG German Mental Retardation Network (MRNET)*
			Symposium IV – Animal, Cellular & Tissue Models	
249	P-4-1	Puk, Oliver	*Aca12* and *Aca23* - two novel mouse models for microphakia and corneal dystrophies	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
250	P-4-2	Dalke, Claudia	"Sighted C3H" mice in the vision screen module of the GMC: Identification of a novel mutation site	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
251	P-4-3	Prehn, Cornelia	metaP: Introducing metabolomic platform at the Helmholtz Zentrum München	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*

Page	Abstract	Submitting Author	Abstract Title	Consortium
252	P-4-4	Prehn, Cornelia	Steroid metabolism screen	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
253	P-4-5	Maier, Holger	MausDB: the German Mouse Clinic open source phenotype data and mouse management system	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
254	P-4-6	Hans, Wolfgang	New mouse models and mechanisms for bone and cartilage disorders	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
255	P-4-7	Hagn, Michael	EMMA - The European Mouse Mutant Archive	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
256	P-4-8	Bergmann, Silke	The HZI infection challenge platform for mutant mice: development of new models and procedures	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
257	P-4-9	Tost, Monica	The pathology screen in the German Mouse Clinic	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
258	P-4-10	Lengger, Christoph	New database-driven tools for cryo sample and workflow management	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
259	P-4-11	Ganguly, Koustav	Superoxide dismutase 3, extracellular (SOD3) and lung function in mice	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
260	P-4-12	Rozman, Jan	Metabolic phenotyping of an obese mutant mouse line	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
261	P-4-13	Neschen, Susanne	A comprehensive approach to identify early derangements in metabolic pathways involved in type 2 diabetes pathophysiology in mouse models	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
262	P-4-14	Zeh, Ramona	Neurological and molecular biological characterization of the mutant mouse line Tom40, the protein that comprises the general import pore of mitochondria	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
263	P-4-15	Raess, Michael	Infrafrontier - the European infrastructure for phenotyping and archiving of model mammalian genomes	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
264	P-4-16	Kemter, Elisabeth	Uromodulin-storage disease in an ENU-induced mutant mouse line	*IG German Mouse Clinic - Deciphering Comorbidity in*

Page	Abstract	Submitting Author	Abstract Title	Consortium
				Human Disease Models
265	P-4-17	Hoelzlwimmer, Gabriele	Comparative histology of inflammatory bowel diseases (IBD) in mice: TNFdARE mutant and Interleukin-10 knockout and mice	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
266	P-4-18	Lücking, Christoph	Proteasomal inhibition reduces *parkin* mRNA in PC12 and SH-SY5Y cells	*IG Functional Genomics of Parkinson*
267	P-4-19	Kahle, Philipp	Regulation of astrocyte inflammatory responses by the parkinson's disease - associated gene DJ-1	*IG Functional Genomics of Parkinson*
268	P-4-20	Marcus, Katrin	Differential proteome analysis of transgenic A53T-alpha-synuclein mice as a model of familial Parkinson's disease	*IG Functional Genomics of Parkinson*
269	P-4-21	Turck, Chris	Strategies for biomarker discovery - from differential expression to metabolites to pathways	*IG Molecular Causes of Major Mood Disorders and Schizophrenia (MooDS)*
270	P-4-22	Walser, Sandra	Functional validation of P2RX7 as a susceptibility marker for depression using humanized mouse mutants	*IG Molecular Causes of Major Mood Disorders and Schizophrenia (MooDS)*
271	P-4-23	Otte, David	Behavioral changes in G72/G30 transgenic mice	*IG Molecular Causes of Major Mood Disorders and Schizophrenia (MooDS)*
272	P-4-24	Schäfer, Reinhold	Perturbation of oncogenic signalling and transcriptional control - an integrated study combining RNA interference and expression profiling	*IG Systems Biology of Genetic Diseases (Mutanom)*
273	P-4-25	Blaich, Stephanie	Identification of novel effector genes for malignant melanoma via recombinant cancer cell technology	*IG Systems Biology of Genetic Diseases (Mutanom)*
274	P-4-26	Mollenhauer, Jan	Construction and use of recombinant isogenic cell libraries in functional genomics	*IG Systems Biology of Genetic Diseases (Mutanom)*
275	P-4-28	Deubzer, Hedwig	Identification of neuroblastoma stem cells	*IG Neuroblastoma Genome Interaction Network*
276	P-4-29	Stermann, Alexander	The development of a new murine *MYCN* overexpressing neuroblastoma cell line	*IG Neuroblastoma Genome Interaction Network*
277	P-4-30	Beck, Heinz	Transcriptional upregulation of $Ca_V3.2$ mediates epileptogenesis in chronic epilepsy	*IG Epilepsy and Migraine Integrated Network (EMINet)*
278	P-4-31	Neu, Axel	Kv7/M-type potassium channels are critical determinants of neuronal network activity in neonatal mouse brain	*IG Epilepsy and Migraine Integrated Network (EMINet)*
279	P-4-32	Kacprzyk, Lukasz	Characterization of novel prostate cancer genes by targeted functional genomics	*IG Integrated Genome Network of Prostate Cancer*
280	P-4-33	Hubner, Norbert	Towards a molecular description of cardiovascular and metabolic disorders in experimental rat models	*IG Genetics of Heart Failure*
281	P-4-34	Just, Steffen	The zebrafish as a convenient animal model to study repolarization	*IG Genetics of Heart Failure*

Page	Abstract	Submitting Author	Abstract Title	Consortium
			disorders	
282	P-4-35	Frank, Derk	Deficiency for Calsarcin-2 increases exercise capacity in vivo by calcineurin/NFAT activation	*IG Genetics of Heart Failure*
283	P-4-36	Frank, Derk	Dyxin/Lmcd1 mediates cardiac hypertrophy both *in vitro* and *in vivo*	*IG Genetics of Heart Failure*
284	P-4-37	Thomas, Roman	An integrated functional genomics approach to systematically link drug activity in non-small cell lung cancer to genetic aberrations	*IG Deciphering Oncogene Dependencies*
285	P-4-38	Sos, Martin	PTEN loss in EGFR mutated non-small cell lung cancer activates EGFR and Akt, thereby contributing to an erlotinib-resistant phenotype	*IG Deciphering Oncogene Dependencies*
286	P-4-39	Wagener, Asja	High food intake and altered lipid metabolism are causes of obesity in the BFMI860 line	*IG Molecular Mechanisms in Obesity*
287	P-4-40	Weiler, Markus	Irradiation-enhanced mammalian target of rapamycin (mTOR)-targeted glioblastoma therapy with CCI-779 (temsirolimus)	*IG Brain Tumor Network*
288	P-4-41	Heeger, Christian	Chondrocyte-like cells in vascular calcification originate from the bone marrow and not from the local vessel wall in LDL-receptor knockout mice	*IG Genomics of Atherosclerosis*
289	P-4-42	Vogt -Weisenhorn, Daniela	DJ-1 deficient mice show reduced numbers of VTA dopaminergic neurons and exhibit cognitive impairments	*IG Neurodegenerative Diseases Networks (NeuroNet)*
290	P-4-43	Friedel,Roland	A library of conditional mutations in mouse embryonic stem cells for the functional analysis of the mammalian genome (EUCOMM)	*IG From Disease Genes to Protein Pathways (DiGTOP)*
291	P-4-44	Wagner, Steve	Circulating tumor cells: quantification, molecular characterization and future prospects	*IG Cellular Systems Genomics in Health and Disease*
292	P-4-45	Till, Andreas	From genetic findings to functional implications - experimental concepts for the comprehensive analysis of genetic variants	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
293	P-4-46	Rosenstiel, Philip	Pathways & gene networks: Innate immunity and barrier function	*IG Systematic Genomics of Chronic Inflammatory Barrier Diseases*
294	P-4-47	Garratt, Alistair	Function of BACE1 and Neuregulins in the developing and adult nervous system	*IG Gene Identification and Functional Analyses in Alzheimer's Disease*
			Symposium V – Genomic / Environmental Interaction	
299	P-5-1	Kolz, Melanie	Association between variations in the *TLR4* gene and incident type 2 diabetes is modified by the ratio of total cholesterol to HDL-cholesterol	*IG Genomics of Atherosclerosis*
300	P-5-2	Peters, Annette	Air pollution and inflammtion: Gene-environment interactions in myocardial infarction survivors	*IG Genomics of Atherosclerosis*
301	P-5-3	Wolff-Muscate, Annemarie	Establishment of a psychophysical stress challenge in the German Mouse Clinic	*IG German Mouse Clinic - Deciphering Comorbidity in*

Page	Abstract	Submitting Author	Abstract Title	Consortium
				Human Disease Models
302	P-5-4	Glasl, Lisa	Olfactory function in genetic mouse models of Parkinson's disease	*IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models*
303	P-5-5	Priller, Josef	Classification of phenotype-to-genotype relationships for neurodegenerative diseases	*IG Neuronet*
304	P-5-6	Gallinat, Jürgen	The concept of endophenotypes in psychiatric diseases	*IG Genetics of Alcohol Addiction*
			Symposium VI – Transfer from Genomics to Application	
309	P-6-1	Yuan, Juping	Characterization and functional analysis of Poloxin: a small molecule inhibitor targeting the polo-box binding domain of Polo-like kinase 1	
310	P-6-2	Sauer, Sascha	Classification and identification of bacteria by mass spectrometry and bioinformatic tools	*IG Molecular Mechanisms in Obesity*
311	P-6-3	Buchholz, Malte	PaCaNet: A translational genome research network in pancreatic cancer	*IG Genome Research Network in Pancreatic Cancer*
312	P-6-4	Bau, Stephan	Targeted next-generation-sequencing by specific capture of multiple genomic loci using low-volume microfluidic DNA-arrays	*IA Subgenome Fractionation for High Throughput Sequencing*
313	P-6-5	Benet-Pagès, Anna	Indexed paired-end next-generation sequencing for medical resequencing demonstrated in patients with congenital hyperinsulinism (CHI)	*IA Subgenome Fractionation for High Throughput Sequencing*
314	P-6-6	Kelkenberg, Sabine	Subgenome fractionation for high throughput sequence analysis	*IA Subgenome Fractionation for High Throughput Sequencing*
315	P-6-7	Schracke, Nadine	Pathway enrichment and next generation re-sequencing of 68 *E. coli* genes using HybSelect™	*IA Subgenome Fractionation for High Throughput Sequencing*
316	P-6-8	Beier, Markus	Subgenome fractionation for high troughput sequencing	*IA Subgenome Fractionation for High Throughput Sequencing*
317	P-6-9	Jankowski, Joachim	Development and validation of new diagnostic, preventive and therapeutic tools for the prevention of cardiovascular diseases and disorders (CVD) in chronic kidney disease (CKD)	*IA New Tools for the Prevention of Cardiovascular Diseases and Disorders in Chronic Kidney Disease*
318	P-6-10	Müller, Oliver	Cell-specific decoy oligodeoxynucleotide delivery to the failing heart	*IA Heart Failure Therapy*
319	P-6-11	Becker,Karl-Friedrich	Protein analysis of formalin-fixed breast cancer tissues for diagnosis, prognosis, and therapy guidance	*IA Protein analysis of formalin-fixed tumor (FFPE) samples*
320	P-6-12	Klopp, Norman	Whole genome and transcriptome amplification in large biobanks	*IA Whole genome and transcriptome amplification in large biobanks*
321	P-6-13	Deubzer, Hedwig	Activation of BMP4 signalling via inhibition of HDAC11 represses neuroblastoma tumorigenicity	*IG Neuroblastoma Genome Interaction Network*

Page	Abstract	Submitting Author	Abstract Title	Consortium
322	P-6-14	Oehme, Ina	Histone deacetylase 8 in neuroblastoma tumorigenesis	*IG Neuroblastoma Genome Interaction Network*
323	P-6-15	Hussain, Azeemudeen	Revealing novel associations between glycosoaminoglycan degradation and Met signalling in cancer	*IG Cellular Systems Genomics in Health and Disease*
324	P-6-16	Wang-Sattler, Rui	Metabolic profiling reveals distinct variations linked to nicotine consumption in humans - first results from the KORA study	*IG Genetics of Alcohol Addiction*
325	P-6-17	Liao, Yunxiang	Molecular correlates of age-dependent seizures in a neonatal-infantile epilepsy	*IG Epilepsy and Migraine Integrated Network (EMINet)*
326	P-6-18	Joberty, Gerard	Identification of potent and selective PI3Kg inhibitors using Kinobeads™ proteomics	*IG Systems Biology of Genetic Diseases (Mutanom)*
327	P-6-19	Eils, Juergen	iCHIP- central translational database for the brain tumor network	*IG Brain Tumor Network*

National Genome Research Network

List of poster abstracts

sorted by submitting author

Submitting Author	Abstract	Page	Abstract-Titel	Poster Session
Adler, Thure	P-2-11	223	Immuno-phenotyping at the German Mouse Clinic. The clustering of T cell subsets.	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Aherrahrou, Zouhair	P-1-31	161	No association between the connexin37 gene polymorphism C1019T and myocardial infarction in a German population	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Aherrahrou, Zouhair	P-1-32	162	Association of SNP rs671699 in the connexion 37 gene with coronary artery calcification	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Anastasov, Natasa	P-3-8	242	NPM-ALK kinase activity influences miRNA expression in ALK+ Anaplastic Large Cell Lymphoma (ALCL)	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Barth, Alexander	P-1-46	176	Identification of QTLs influencing anxiety and depression in mice	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Bau, Stephan	P-6-4	312	Targeted next-generation-sequencing by specific capture of multiple genomic loci using low-volume microfluidic DNA-arrays	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Beck, Heinz	P-4-30	277	Transcriptional upregulation of $Ca_V3.2$ mediates epileptogenesis in chronic epilepsy	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Becker, Albert	P-3-2	236	Transcriptional key mechanisms in epilepsy: Induction of T-type calcium channel $Ca_V3.2$ expression by zinc	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Becker,Karl-Friedrich	P-6-11	319	Protein analysis of formalin-fixed breast cancer tissues for diagnosis, prognosis, and therapy guidance	Saturday,13.12.2008, 10:45 am - 12:45 pm
Beier, Markus	P-6-8	316	Subgenome fractionation for high troughput sequencing	Saturday,13.12.2008, 10:45 am - 12:45 pm
Benet-Pagès, Anna	P-6-5	313	Indexed paired-end next-generation sequencing for medical resequencing demonstrated in patients with congenital hyperinsulinism (CHI)	Saturday,13.12.2008, 10:45 am - 12:45 pm
Bergmann, Silke	P-4-8	256	The HZI infection challenge platform for mutant mice: development of new models and procedures	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Bettecken, Thomas	P-1-49	179	No evidence for DUP25 in anxiety patients, as judged by molecular karyotyping	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Bisping, Egbert	P-1-20	150	Applicability and relationship of E/e', LAVI, age, natriuretic peptides and hypertrophic markers in diastolic dysfunction and diastolic heart failure	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Bisping, Egbert	P-1-21	151	Genome-wide association analysis of left ventricular hypertrophy and diastolic heart failure	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Blaich, Stephanie	P-4-25	273	Identification of novel effector genes for malignant melanoma via recombinant cancer cell technology	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Bolze, Florian	P-1-55	185	The premature nonsense mutation W16X in the melanocortin-4-receptor gene causes obesity in mice	Friday, 12.12.2008, 1:00 pm - 3:00 pm

Submitting Author	Abstract	Page	Abstract-Titel	Poster Session
Boutros, Michael	P-1-41	171	Systematic dissection of Wnt signaling networks	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Boutros, Michael	P-2-3	215	Large-scale rna interference screens and high-content analysis to dissect cellular pathways	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Brase, Jan Christoph	P-1-37	167	Antibody-based signal amplification improves specific target detection on reverse phase protein arrays	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Büchel, Finja	P-1-8	138	ProDGe - a sequence and protein interaction viewer	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Buchholz, Malte	P-6-3	311	PaCaNet: A translational genome research network in pancreatic cancer	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Butuzova, Kateryna	P-1-34	164	Characterisation of a new ENU induced mouse model for Polycytemia Vera	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Dalke, Claudia	P-4-2	250	"Sighted C3H" mice in the vision screen module of the GMC: Identification of a novel mutation site	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Deubzer, Hedwig	P-4-28	275	Identification of neuroblastoma stem cells	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Deubzer, Hedwig	P-6-13	321	Activation of BMP4 signalling via inhibition of HDAC11 represses neuroblastoma tumorigenicity	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Dittmer, Alexandra	P-1-64	194	Interactions of viral and cellular miRNAs in the MCMV system	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Dräger, Andreas	P-2-13	225	SBML2LaTeX: Conversion of SBML files into human-readable reports	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Dräger, Andreas	P-2-14	226	Modeling metabolic networks: a comparison of rate laws in combination with various parameter optimization strategies	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Dräger, Andreas	P-2-15	227	SBMLsqueezer: a CellDesigner plug-in to generate kinetic rate equations for biochemical networks	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Drews, Eva	P-1-13	143	QTL analysis of endophenotypes related to alcoholism	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Eck, Sebastian	P-1-33	163	Analysis of copy number variation in a population based study using high density SNP microarrays	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Eifert, Sandra	P-1-23	153	Systematic pathway-analysis of Kinesin Protein Family (KIF) using genome-wide SNP data in patients with myocardial infarction: Genetic variation in KIF17 gene associates with myocardial infarction	Friday, 12.12.2008, 1:00 pm - 3:00 pm

Submitting Author	Abstract	Page	Abstract-Titel	Poster Session
Eifert, Sandra	P-1-24	154	First genome-wide association study in patients underwent Coronary Artery Bypass Grafting (CABG) under gender specific perspectives	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Eils, Juergen	P-6-19	327	iCHIP- central translational database for the brain tumor network	Saturday, 13.12.2008, 10:45 am - 12:45 pm
El Gammal, Alexander	P-1-39	169	Chromosome 8p deletions and 8q gains are associated with tumor progression and poor prognosis in prostate cancer	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Elstner, Matthias	P-1-11	141	Gene expression analysis in dopaminergic neurons of the substantia nigra reveals candidate genes and differentially regulated pathways in Parkinson disease	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Emeny, Rebecca	P-1-47	177	Single nucleotide polymorphism associations with Type-D personality in the general population; findings from the KORA K-500-substudy	Friday, 12.12.2008, 1:00 pm - 3:00 pm
End, Caroline	P-1-79	208	Analysis of innate defence factors in esophageal and gastric cancer	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Erdmann, Jeanette	P-1-22	152	Novel susceptibility locus for coronary artery disease on chromosome 3q22.3	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Esparza Gordillo, Jorge	P-1-73	202	Genome-wide association study for atopic dermatitis	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Filiou, Michaela	P-2-4	216	Biomarker discovery via stable isotope metabolic labeling of a trait anxiety mouse model	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Fisher, Eva	P-1-61	191	The fat-mass and obesity associated (*FTO)* rs9939609 single nucleotide polymorphism is associated with high C-reactive protein levels independently from obesity indices in EPIC-Potsdam	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Flachsbart, Friederike	P-1-67	197	Systematic detection of genetic variation associated with exceptional life expectancy in humans	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Fontaine, Jean-Fred	P-2-18	230	Ranking the biomedical literature for optimised experimental designs	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Frank, Derk	P-4-35	282	Deficiency for Calsarcin-2 increases exercise capacity in vivo by calcineurin/NFAT activation	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Frank, Derk	P-4-36	283	Dyxin/Lmcd1 mediates cardiac hypertrophy both *in vitro* and *in vivo*	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Franke, André	P-1-76	205	Sequence variants in IL10, ARPC2 and multiple other loci contribute to ulcerative colitis susceptibility	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Friedel, Susann	P-1-56	186	NGFN^{PLUS}-Network "molecular mechanisms in obesity"	Friday, 12.12.2008, 1:00 pm - 3:00 pm

Submitting Author	Abstract	Page	Abstract-Titel	Poster Session
Friedel, Roland	P-4-43	290	A library of conditional mutations in mouse embryonic stem cells for the functional analysis of the mammalian genome (EUCOMM)	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Gallinat, Jürgen	P-5-6	304	The concept of endophenotypes in psychiatric diseases	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Ganguly, Koustav	P-4-11	259	Superoxide dismutase 3, extracellular (SOD3) and lung function in mice	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Garratt, Alistair	P-4-47	294	Function of BACE1 and Neuregulins in the developing and adult nervous system	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Gieger, Christian	P-1-19	149	A genome wide association study reveals SLC2A9 as a major gene for uric acid levels with pronounced sex-specific effects	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Glasl, Lisa	P-5-4	302	Olfactory function in genetic mouse models of Parkinson's disease	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Gloeckner, Christian	P-1-9	139	The Parkinson disease-associated protein kinase LRRK2 shares sequence homology with MAP3K and phosphorylates classical MAP3K targets, *in vitro*	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Grallert, Harald	P-1-52	182	Genetic variation in the *Resistin* locus and components of the metabolic syndrome in 5100 subjects	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Grothe, Jessica	P-1-57	187	Obesity relevant melanocortin-4-receptor gene variants and identity by descent: Analysis of single nucleotide polymorphisms - not only in the context of association studies	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Hagn, Michael	P-4-7	255	EMMA - The European Mouse Mutant Archive	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Hans, Wolfgang	P-4-6	254	New mouse models and mechanisms for bone and cartilage disorders	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Heeger, Christian	P-4-41	288	Chondrocyte-like cells in vascular calcification originate from the bone marrow and not from the local vessel wall in LDL-receptor knockout mice	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Henjes, Frauke	P-2-10	222	Quantitative proteomics of growth factor receptor and hormone receptor signaling	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Hiersche, Milan	P-2-12	224	Analysis of genetic factors in disease susceptibility: An integrative systems biology concept	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Hinney, Anke	P-1-51	181	Gastric inhibitory polypeptide receptor: Association analyses of several polymorphisms in large study groups pertaining to obesity	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Hinney, Anke	P-1-54	184	Large family-based genome-wide association scan for early onset extreme obesity	Friday, 12.12.2008, 1:00 pm - 3:00 pm

Submitting Author	Abstract	Page	Abstract-Titel	Poster Session
Hoehe, Margret	P-1-42	172	NGFN-Plus IG: MHC haplotype sequencing: An integrated approach to common disease	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Hoelzlwimmer, Gabriele	P-4-17	265	Comparative histology of inflammatory bowel diseases (IBD) in mice: TNFdARE mutant and Interleukin-10 knockout and mice	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Hofmann, Sylvia	P-1-74	203	Identification of *ANXA11* as a novel risk locus for saroidosis by a genomewide association study	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Horsch, Marion	P-2-7	219	Systematic gene expression profiling of a series of mouse models reveals co-expressed genes	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Hosp, Fabian	P-2-1	213	Identification and quantification of protein-protein interactions in neurodegenerative diseases using mass spectrometry	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Hubner, Norbert	P-4-33	280	Towards a molecular description of cardiovascular and metabolic disorders in experimental rat models	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Huse, Klaus	P-1-70	199	Clinical impact of defensin copy number variation	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Hussain, Azeemudeen	P-6-15	323	Revealing novel associations between glycosoaminoglycan degradation and Met signalling in cancer	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Jankowski, Joachim	P-6-9	317	Development and validation of new diagnostic, preventive and therapeutic tools for the prevention of cardiovascular diseases and disorders (CVD) in chronic kidney disease (CKD)	Saturday, 13.12.2008 10:45 am - 12:45 pm
Joberty, Gerard	P-6-18	326	Identification of potent and selective PI3Kg inhibitors using Kinobeads™ proteomics	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Just, Steffen	P-4-34	281	The zebrafish as a convenient animal model to study repolarization disorders	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Kacprzyk, Lukasz	P-4-32	279	Characterization of novel prostate cancer genes by targeted functional genomics	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Kahle, Philipp	P-4-19	267	Regulation of astrocyte inflammatory responses by the parkinson's disease -associated gene DJ-1	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Katus, Hugo	P-1-16	146	Chromosome 9q21 as a new major susceptibility locus for dilated cardiomyopathy	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Kelkenberg, Sabine	P-6-6	314	Subgenome fractionation for high throughput sequence analysis	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Kemter, Elisabeth	P-4-16	264	Uromodulin-storage disease in an ENU-induced mutant mouse line	Friday, 12.12.2008, 1:00 pm - 3:00 pm

Submitting Author	Abstract	Page	Abstract-Titel	Poster Session
Khuseyinova, Natalie	P-1-27	157	No association between C-reactive Protein (CRP) gene polymorphisms, CRP haplotypes and incident type 2 diabetes mellitus (T2DM) in middle-aged men and women: results from the MONICA/KORA Augsburg case-cohort study, 1984-2002	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Kiełbasa, Szymon	P-3-3	237	Conservation of transcriptional autoregulatory feedback loop in vertebrates	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Kloiber, Stefan	P-1-45	175	Variations in Tryptophan Hydroxylase 2 leading to decreased serotonergic activity are associated with elevated risk for metabolic syndrome in depression	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Klopp, Norman	P-6-12	320	Whole genome and transcriptome amplification in large biobanks	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Knöll, Ralph	P-1-18	148	Novel Z-disk proteins and cardiac-mechanosensation	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Koenig, Wolfgang	P-1-25	155	No association between monocyte chemoattractant protein-1 (MCP-1) gene polymorphisms and incident type 2 diabetes mellitus (T2DM) in middle-aged men and women: results from the MONICA/KORA Augsburg case-cohort study, 1984-2002	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Koenig, Wolfgang	P-1-26	156	Monocyte chemoattractant protein-1 (MCP-1) gene polymorphisms, MCP-1 plasma levels and incident coronary heart disease (CHD) in middle-aged men and women: Results from the MONICA/KORA Augsburg case-cohort study, 1984-2002	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Kolz, Melanie	P-5-1	299	Association between variations in the *TLR4* gene and incident type 2 diabetes is modified by the ratio of total cholesterol to HDL-cholesterol	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Korf, Ulrike	P-2-8	220	Protein microarrays as tool for cancer systems biology	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Kuner, Ruprecht	P-1-65	195	Sample preparation for an integrated analysis of genomic, transcriptomic, and proteomic markers from the same tissue source	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Lange, Bodo	P-2-5	217	IG mutanom - systems biology of genetic diseases	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Lascorz, Jesus	P-1-40	170	Genome-wide association study for colorectal cancer in German familial cases and replication in independent cohorts	Friday, 12.12.2008, 1:00 pm - 3:00 pm

Submitting Author	Abstract	Page	Abstract-Titel	Poster Session
Lawerenz, Chris	P-2-17	229	iCHIP- sustainable data pool services for Neuroblastoma	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Lehrach, Hans	P-1-78	207	The German participation in the 1000 Genomes Project	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Lengger, Christoph	P-4-10	258	New database-driven tools for cryo sample and workflow management	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Liao, Yunxiang	P-6-17	325	Molecular correlates of age-dependent seizures in a neonatal-infantile epilepsy	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Lohmann, Katja	P-1-63	193	Heterozygous *ATP13A2* variants in patients with early-onset Parkinson disease and controls	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Lucae, Susanne	P-1-44	174	A genome-wide association study in major depression reveals association of SNPs on chromosome 12q21.31	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Lücking, Christoph	P-4-18	266	Proteasomal inhibition reduces *parkin* mRNA in PC12 and SH-SY5Y cells	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Maier, Holger	P-4-5	253	MausDB: the German Mouse Clinic open source phenotype data and mouse management system	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Maljevic,Snezana	P-1-6	136	A trafficking defective $K_V7.2$ mutation causing neonatal seizures	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Malterer, Georg	P-3-7	241	Identification of targets for KSHV-encoded miRNAs	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Malzahn, Dörthe	P-1-14	144	Longitudinal gene-gene and gene-time effects on body mass index for variants near *INSIG2* and in the *MC4R* gene	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Manke, Thomas	P-3-4	238	Quantitative models and prediction of regulatory interactions	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Mannsperger, Heiko	P-1-35	165	Large Scale Quantitative Analysis of Tumor Samples using Protein Microarrays	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Marcus, Katrin	P-4-20	268	Differential proteome analysis of transgenic A53T-alpha-synuclein mice as a model of familial Parkinson's disease	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Medack, Anja	P-1-28	158	Comperative mapping of linkage and association results in myocardial infarction	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Minner, Sarah	P-1-38	168	Low level HER2 overexpression is associated with rapid tumor cell proliferation and poor prognosis in prostate cancer	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Mollenhauer, Jan	P-4-26	274	Construction and use of recombinant isogenic cell libraries in functional genomics	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Morkel, Markus	P-1-43	173	Identification of modifiers of intestinal tumor formation and progression using mouse B6/PWD chromosome substitution strains	Friday, 12.12.2008, 1:00 pm - 3:00 pm

Submitting Author	Abstract	Page	Abstract-Titel	Poster Session
Mössner, Rainald	P-1-48	178	Systematic investigation of the molecular causes of major mood disorders and schizophrenia (MooDS): SP3: Genomics of Schizophrenia	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Müller, Martina	P-1-30	160	A genome-wide association analysis of HDL-cholesterol in the population-based KORA study sheds new light on intergenic regions	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Müller, Oliver	P-6-10	318	Cell-specific decoy oligodeoxynucleotide delivery to the failing heart	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Muro, Enrique	P-3-5	239	Pseudogenes as a source of trans-NAT seeds	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Neschen, Susanne	P-4-13	261	A comprehensive approach to identify early derangements in metabolic pathways involved in type 2 diabetes pathophysiology in mouse models	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Neu, Axel	P-4-31	278	Kv7/M-type potassium channels are critical determinants of neuronal network activity in neonatal mouse brain	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Nitz, Barbara	P-1-12	142	Genome wide association study and analysis of candidate genes on nicotine dependence	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Nothnagel, Michael	P-1-71	200	A comprehensive evaluation of SNP genotype imputation	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Oehme, Ina	P-6-14	322	Histone deacetylase 8 in neuroblastoma tumorigenesis	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Otte, David	P-4-23	271	Behavioral changes in G72/G30 transgenic mice	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Peters, Annette	P-5-2	300	Air pollution and inflammtion: Gene-environment interactions in myocardial infarction survivors	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Poschmann, Gereon	P-1-59	189	Proteomic profiling of mouse hypothalamus in strains susceptible or resistant to diet-induced obesity	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Prehn, Cornelia	P-4-3	251	metaP: Introducing metabolomic platform at the Helmholtz Zentrum München	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Prehn, Cornelia	P-4-4	252	Steroid metabolism screen	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Preuss, Christoph	P-1-17	147	Evolutionary dynamics of gene cluster rearrangements associated with complex diseases	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Priller, Josef	P-5-5	303	Classification of phenotype-to-genotype relationships for neurodegenerative diseases	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Puk, Oliver	P-4-1	249	*Aca12* and *Aca23* - two novel mouse models for microphakia and corneal dystrophies	Friday, 12.12.2008, 1:00 pm - 3:00 pm

Submitting Author	Abstract	Page	Abstract-Titel	Poster Session
Radlwimmer, Bernhard	P-1-1	131	Global analyses of molecular differentiation pathways in brain-tumor stem cells	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Raess, Michael	P-4-15	263	Infrafrontier - the European infrastructure for phenotyping and archiving of model mammalian genomes	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Riechers, Sean-Patrick	P-2-6	218	Generation and systematic analysis of protein-protein interaction networks for cytoplasmic protein-tyrosine kinases in human cancer	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Rivera Brugués,Núria	P-3-10	244	Identification of disease-related copy number variation (CNV) in patients with mental retardation by high-dense SNP genotyping microarrays	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Rodriguez, Elke	P-1-68	198	Analysis of gene-gene interaction within the filaggrin pathway	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Rosenstiel, Philip	P-4-46	293	Pathways & gene networks: Innate immunity and barrier function	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Rößler, Paula	P-1-50	180	Gene-Gene interaction between *APOA5* and *USF1*: Two candidate genes for the metabolic syndrome	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Rozman, Jan	P-4-12	260	Metabolic phenotyping of an obese mutant mouse line	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Sahin, Özgur	P-1-2	132	Identification of oncomirs targeting feedback regulators of EGFR signaling	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Sahin, Özgur	P-2-9	221	Modeling ERBB receptor-regulated G1/S transition to find novel targets for de novo trastuzumab resistance	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Sauer, Sascha	P-3-1	235	Modulating the action of nuclear receptors by natural products	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Sauer, Sascha	P-6-2	310	Classification and identification of bacteria by mass spectrometry and bioinformatic tools	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Sauter, Wiebke	P-1-4	134	Case-control study of genetic susceptibility in early onset lung cancer: Investigation of *Matrix Metalloproteinase 1* (*MMP1*)	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Schäfer, Helmut	P-1-53	183	Planning genome wide association studies under limited budget	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Schäfer, Reinhold	P-4-24	272	Perturbation of oncogenic signalling and transcriptional control - an integrated study combining RNA interference and expression profiling	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Schedel, Michaela	P-1-75	204	Allele-specific NF-kB-binding alters STAT6 expression and contributes to genetic IgE control	Friday, 12.12.2008, 1:00 pm - 3:00 pm

Submitting Author	Abstract	Page	Abstract-Titel	Poster Session
Scherag, André	P-1-58	188	Novel genetic variants for obesity identified in a joint analysis of two genome-wide association scans for early onset extreme	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Schracke, Nadine	P-6-7	315	Pathway enrichment and next generation re-sequencing of 68 *E. coli* genes using HybSelect™	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Schreiber, Stefan	P-1-66	196	Systematic full resequencing of patient populations to assess genetic susceptibility in complex diseases	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Schubert, Walter	P-2-16	228	Human TOPONOME project: Progress report	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Schulte, Johannes	P-1-62	192	MicroRNAs in the pathogenesis of neuroblastoma	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Schulz, Angela	P-1-15	145	Conversion of the salt-resistant phenotype of spontaneously hypertensive rats into a salt-sensitive phenotype leads to severe cardiac hypertrophy in a new double-consomic rat model	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Sharma, Manu	P-1-10	140	Genome-wide association study in Parkinson's disease reveals strong association signals in the SNCA AND MAPT genes	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Sos, Martin	P-4-38	285	PTEN loss in EGFR mutated non-small cell lung cancer activates EGFR and Akt, thereby contributing to an erlotinib-resistant phenotype	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Stermann, Alexander	P-4-29	276	The development of a new murine *MYCN* overexpressing neuroblastoma cell line	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Suttner, Kathrin	P-1-72	201	Genetic variants in the transcription factors T-bet, HLX1 and GATA3 and their functional role in the development of asthma	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Thomas, Roman	P-4-37	284	An integrated functional genomics approach to systematically link drug activity in non-small cell lung cancer to genetic aberrations	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Till, Andreas	P-4-45	292	From genetic findings to functional implications - experimental concepts for the comprehensive analysis of genetic variants	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Todt, Unda	P-1-5	135	New genetic evidence for involvement of the dopamine system in migraine with aura	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Tost, Monica	P-4-9	257	The pathology screen in the German Mouse Clinic	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Tschulena, Ulrich	P-1-3	133	A novel large-scale screen to identify modulators of miR-21	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Tschulena, Ulrich	P-3-6	240	A genome-wide RNAi screen to identify modulators of human P38 signalling	Friday, 12.12.2008, 1:00 pm - 3:00 pm

Submitting Author	Abstract	Page	Abstract-Titel	Poster Session
Turck, Chris	P-4-21	269	Strategies for biomarker discovery - from differential expression to metabolites to pathways	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Ummanni, Ramesh	P-1-36	166	Identification and characterization of new clinically applicable target proteins in prostate cancer	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Vogel, Heike	P-1-60	190	*Nob3* - A major QTL for obesity on mouse chromosome 1	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Vogt -Weisenhorn, Daniela	P-4-42	289	DJ-1 deficient mice show reduced numbers of VTA dopaminergic neurons and exhibit cognitive impairments	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Wagener, Asja	P-4-39	286	High food intake and altered lipid metabolism are causes of obesity in the BFMI860 line	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Wagner, Steve	P-4-44	291	Circulating tumor cells: quantification, molecular characterization and future prospects	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Walser, Sandra	P-4-22	270	Functional validation of P2RX7 as a susceptibility marker for depression using humanized mouse mutants	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Wang-Sattler, Rui	P-6-16	324	Metabolic profiling reveals distinct variations linked to nicotine consumption in humans - first results from the KORA study	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Wanker, Erich	P-2-2	214	Detecting novel connections between neurodegenerative diseases: the NGFN-Plus consortium IG NeuroNet	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Weber, Yvonne	P-1-77	206	A GLUT1 mutation in patients with constant spastic paraplegia and paroxysmal dyskinesia	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Weiler, Markus	P-3-9	243	The role of hypoxia-induced N-myc down-regulated gene 1 (NDRG1) in glioma biology	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Weiler, Markus	P-4-40	287	Irradiation-enhanced mammalian target of rapamycin (mTOR)-targeted glioblastoma therapy with CCI-779 (temsirolimus)	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Wolff-Muscate, Annemarie	P-5-3	301	Establishment of a psychophysical stress challenge in the German Mouse Clinic	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Wurst, Wolfgang	P-1-7	137	From Disease Genes to Protein Pathways: the DIGTOP project	Friday, 12.12.2008, 1:00 pm - 3:00 pm
Yuan, Juping	P-6-1	309	Characterization and functional analysis of Poloxin: a small molecule inhibitor targeting the polo-box binding domain of Polo-like kinase 1	Saturday, 13.12.2008, 10:45 am - 12:45 pm
Zeh, Ramona	P-4-14	262	Neurological and molecular biological characterization of the mutant mouse line Tom40, the protein that comprises the general import pore of mitochondria	Friday, 12.12.2008, 1:00 pm - 3:00 pm

Submitting Author	Abstract	Page	Abstract-Titel	Poster Session
Zeller, Tanja	P-1-29	159	From genomics to transcriptomics - genome-wide association - and expressionanalyses in the population-based Gutenberg Heart Study	Friday, 12.12.2008, 1:00 pm - 3:00 pm

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Oral presentation abstracts

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Symposium I

Genomics of Common Disease

Opening Keynote Presentation

Symposium I - Genomics of Common Disease O-1-1

Genetics of CAD (coronary artery disease): an update

Nilesh Samani

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Coronary artery disease is the commonest cause of premature mortality and morbidity in the developed world. It has a significant genetic component which has been recognised for over a 100 years. Dissecting the genetic basis of CAD, as with that of other complex traits, has been challenging. In this talk, I will review the progress that has been made in elucidating the genetic architecture of CAD and especially focus on the findings emerging from genome-wide association analysis of CAD. I will discuss the novel insights these findings are providing on our understanding of the pathogenesis of CAD and their potential application for its prediction and prevention and for development of novel treatments. I will discuss the work that lies ahead.

Common variants at ten loci modulate the QT interval duration in individuals of European ancestry: the QTSCD consortium

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The QT interval, a measure of cardiac repolarization, predisposes to ventricular tachycardia and sudden cardiac death (SCD) when prolonged or shortened. Previously, a common variant in *NOS1AP (CAPON)* influencing QT interval was mapped in a European population. We now analyze genome-wide association data from five European ancestry samples (ARIC, KORA, SardiNIA, GenNOVA and HNR, *N* = 15,842). We confirm the *NOS1AP* association (P=1.63x10^{-35}) and identify nine additional loci at P<5x10^{-8}. Four loci map near the monogenic long QT syndrome genes *KCNQ1*, *KCNH2*, *SCN5A* and *KCNJ2*. Two other loci map to 1q22-q24 (P=2.18 x10^{-12}) and to 6q22-q23 (P =1.97x10^{-16}). The remaining three loci in 1p36 (P =3.57x10^{-9}), in 16p13 (P=2.92x10^{-8}) and in 16q21 (P=1.26x10^{-12}) have not been previously implicated in human myocardial electrophysiology. Taken together genetic variation at these 10 loci explained 3.3% of corrected QT interval variation across all studies. The ~8% of individuals carrying 14 or more QT prolonging alleles had an OR of 2.52 to have prolonged QT by clinical standards when compared to the ~10% of individuals carrying 8 or less alleles (95% CI 1.74-3.66, P = 4.83 x 10^{-7}). These results provide new insights into myocardial electrophysiology and provide novel candidate genes for ventricular arrhythmias and SCD.

Genome-wide association study of alcohol dependence

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Objective: To identify vulnerability genes for alcohol dependence through a genome-wide association (GWA) and replication study in a population of German male inpatients with an early age at onset.

Methods: The GWA study comprised 487 male inpatients with DSM-IV alcohol dependence with an age at onset below 28 years and 1,358 population based control individuals. The replication study included 1,024 male inpatients and 996 age-matched male controls. All individuals were of German descent. 524,396 single nucleotide polymorphisms were tested. All SNPs with $p < 10^{-4}$ were carried on in the replication study. Additional SNPs with at least nominal significance were added to the replication step because they are located in genes which have shown changes in expression in the brain of alcohol dependent rats.

Results and Discussion: The GWA produced 121 SNPs with $p < 10^{-4}$. We included a total of 139 SNPs in the replication step of which 15 SNPs showed association with the same allele. In the pooled analysis the lowest p-values ($p=9.72 \times 10^{-9}$ and 1.69×10^{-8}) were obtained for two closely linked intergenic SNPs on chromosome 2q35, a region which has been implicated in linkage findings on alcohol-related phenotypes. Several SNPs were located in genes, among those are the *ADH1C* and *CDH13* which have been reported to be associated with alcohol dependence. This is the first GWA and replication study which identified a genome-wide significant association in alcohol dependence. Our study demonstrates that the GWA approach can be successfully applied to such a heterogeneous disorder as alcohol dependence when the samples under study are carefully selected for homogeneity.

Large recurrent microdeletions associated with schizophrenia

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Schizophrenia is a severe neuropsychiatric disorder affecting about 1% of the population world-wide. Reduced fecundity places negative selection pressure on risk alleles which may explain in part the difficulties to identify common variants conferring risk to the disease. We therefore hypothesized that rare variants may account for a fraction of the overall genetic risk. In contrast to rare single nucleotide mutations, rare copy number variations (CNVs) can be detected using genome-wide SNP arrays.
In a genome-wide search for CNVs associating with schizophrenia we used a population-based sample to identify *de novo* CNVs by analyzing 9,878 transmissions from parents to offspring. We identified 66 *de novo* CNVs and tested them for association in a sample of 1,433 schizophrenia patients and 33,250 controls. Three deletions at 1q21.1, 15q11.2 and 15q13.3 showing nominal association with schizophrenia in the first sample (phase I) were followed up in a second sample of 3,285 cases and 7,951 controls (phase II). All three deletions significantly associate with schizophrenia and related psychoses in the combined sample (P=2.9×10-5, OR=14.83; P=6.0×10-4, OR=2.73; P=5.3×10-4, OR=11.54, respectively). While the identification of these rare, recurrent, risk variants likely to be under negative selection is important in itself, CNV analysis may also point the way to the identification of additional and more prevalent risk variants in genes and pathways involved in schizophrenia.

Meta-analyses of genome-wide association studies: six new obesity associated loci highlight a neuronal influence on body weight regulation

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Background. Obesity is a major risk factor for severe chronic diseases and accounts for a large part of the morbidity, mortality, and severe economic burdens on health care systems and for individuals. To date, only two common variants (in *FTO* and near *MC4R*) have been shown convincingly to impact body mass index (BMI) at a population level.

Methods: To identify additional loci, we conducted a meta-analysis of genome-wide association (GWA) data analyzing body mass index (BMI) using ~2.4 million imputed or genotyped SNPs in 13 genome-wide association studies including > 32,000 individuals from Germany (KORA), Sweden and Finland (DGI, FUSION), the USA (PLCO, NHS), the UK (WTCCC-T2D, WTCCC-HT, WTCCC-CAD, BC58, NHS, and GEM-EPIC), Switzerland (CoLaus), and Italy (SardiNIA). We followed 35 promising top signals in European ancestry samples from 14 additional studies (N>59,000). We did RT-PCR analysis to examine expression of candidate causal genes in human tissues.

Results: Meta-analysis of GWA studies and follow up association results strongly confirm association of *FTO* ($p = 1 \times 10^{-42}$) and *MC4R* ($p = 8 \times 10^{-19}$) and identifies six novel loci associated with BMI that reach genome wide significance ($p < 5 \times 10^{-8}$): TMEM18, KCTD15, GNPDA2, SH2B1, MTCH2, and NEGR1. In the NEGR1, a 45 kb deletion polymorphism is a candidate causal variant. While the function of some of the likely causal genes near the identified loci are are unknown (TMEM18, KCTD15, MTCH2), several of the likely causal genes' loci (NEGR1, SH2B1, GNPDA2) are highly-expressed or known to act in the central nervous system (CNS) emphasizing, as in rare monogenic forms of obesity, the role of the CNS in predisposition to obesity.

Conclusions and Outlook: Our meta-analysis of GWA studies for body mass index has identified many new variants that give us unprecedented new insights into the biology of obesity in humans and highlight the important role of the central nervous system in regulation of body mass. Further on-going analyses aim at identifying new loci specific to central obesity and on extending the sample size to 100,000 subjects with GWA data.

Genome-wide scan reveals association of psoriasis with IL-23 and NF-kB pathways

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Psoriasis is a common immune mediated disorder that primarily affects the skin, nails, and joints. Disease typically appears in early adult life, and affects from one in fifty to one in a thousand persons worldwide. Genetic factors and environmental triggers both contribute to disease susceptibility, but most of these remain unidentified. To identify genetic loci that contribute to psoriasis susceptibility, we first genotyped 438,670 SNPs in 1,409 European ancestry psoriasis cases and 1,436 controls. Twenty-one SNPs representing loci showing promising evidence of association in the initial scan were followed-up in 5,048 psoriasis cases and 5,041 controls. Our results provide strong support for the association of at least seven genetic loci and psoriasis (for the lead SNP at each of these loci, evidence for association was observed with $p < 5x10^{-4}$ in follow-up samples and $p < 5x10^{-8}$ overall). The loci with confirmed association encode *HLA-C*, three genes involved in IL-23 signaling (*IL23A*, *IL23R* and *IL12B*), two genes that act downstream of TNF-□ and regulate NF-kB signaling (*TNIP1* and *TNFAIP3*), and a set of genes involved in the modulation of Th2 immune responses (*IL4* and *IL13*). Although the proteins encoded in these loci are known to interact biologically, we found no evidence for epistasis between associated SNPs. Our results expand the catalog of genetic loci implicated in psoriasis susceptibility and suggest priority targets for study in other auto-immune disorders.

For the Collaborative Association Study for Psoriasis

Genome-wide scan on total serum IgE levels identifies FCER1A as novel susceptibility locus

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High levels of serum IgE are markers of parasite and helminth exposure. In addition, they are associated with allergic disorders, play a key role in anti-tumoral defence and are crucial mediators of autoimmune diseases. Total IgE is a strongly heritable trait. In a genome wide association study (GWAS) we tested 353,569 SNPs for association with serum IgE levels in 1,530 individuals from the population-based KORA S3/F3 study. Replication was performed in 4 independent population-based study samples (total n=9,769 individuals). Functional variants in the gene encoding the alpha chain of the high affinity receptor for IgE (*FCER1A*) on chromosome 1q23 (rs2251746 and rs2427837) were strongly associated with total IgE levels in all cohorts with *P* values of 1.85×10^{-20} and 7.08×10^{-19} in a combined analysis, and in a post-hoc-analysis showed additional associations with allergic sensitization ($P = 7.78 \times 10^{-4}$ and $P = 1.95 \times 10^{-3}$). The "top" SNP significantly influenced the cell surface expression of FCER1A on basophils, and genome-wide expression profiles indicated an interesting novel regulatory mechanism of FCER1A expression via GATA-2. Polymorphisms within the *RAD50* gene on chromosome 5q31 were consistently associated with IgE levels (*P* values 6.28×10^{-7} - 4.46×10^{-8}) and increased the risk for atopic eczema and asthma. Furthermore, *STAT6* was confirmed as susceptibility locus modulating IgE levels.

In this first GWAS on total IgE *FCER1A* was identified and replicated as new susceptibility locus at which common genetic variation influences serum IgE levels. In addition, variants within the *RAD50* gene might represent additional factors within the cytokine gene cluster on chromosome 5q31, emphasizing the need for further investigations in this intriguing region. Our data furthermore confirm association of *STAT6* variation with serum IgE levels.

National Genome Research Network

Oral presentation abstracts

Symposium II

Systems Biology

Integration of human molecular interactions

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Molecular interactions are key drivers of biological function. Large numbers of interactions for man and other species have been generated, annotated, and made publicly available. Current knowledge of these interactions is dispersed in more than 200 databases, each having a specific focus and data format. Only little effort has so far been undertaken with respect to the integration of these data. Within the SMP Protein of NGFN-2 we have developed ConsensusPathDB (CPDB) a database for integrating heterogeneous human interactions (Kamburov et al., Nucleic Acids Res, doi:10.1093/nar/gkn698). CPDB currently comprises a total of 25,831 distinct physical entities and 73,426 distinct functional interactions covering 1,689 human pathways and integrating twelve different interaction databases with heterogeneous foci. We describe the database schema, the web interface and the methods used for data integration. Furthermore, we describe statistical features of parts of the integrated network and a new method for performing gene enrichment and over-representation analyses.

Constructing a causal protein interaction network for activated MAPK signalling

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The mitogen-activated protein kinase (MAPK) pathway is a key signaling pathway that regulates diverse cellular process in response to various external stimuli. Deregulation of this pathway is a hallmark of several human diseases ranging from cancers to neurodegeneration. To get a global view of the proteins that are involved in MAPK signaling, we performed an automated, Y2H screening to map the interacting partners of the MAPK pathway. Here, we present a MAPK protein-protein interaction (PPI) network, with 2,626 high quality interactions that physically link the MAPK pathway to other cellular proteins. We have also developed a generic computational approach that uses a Naive Bayesian classifier to predict the probable direction of signal flow among the interacting partners. Using this approach, the undirected MAPK network was converted into a directed/activated MAPK network. Specifying the order in which signals propagate in the network enabled the identification of regulatory network motifs that are crucial for signal processing. This enriched network motif profile placed the activated MAPK network within the superfamily of biological information-processing networks. Novel paths that process signaling information and potential regulators of ERK signaling were inferred on the basis of the activated MAPK network. Subsequent validation using a cell-based assay revealed 21 novel regulators of ERK activation. The activated network can be applied to other signaling pathways to predicting how the signal propagates though a densely connected protein network leading to specific cellular responses.

High resolution gene expression profiling for simultaneous kinetic parameter analysis of RNA synthesis and decay

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RNA synthesis and decay govern cellular RNA levels. Microarray analyses carried out today mainly measure RNA abundance. Therefore, changes in total cellular RNA levels can not be attributed to RNA synthesis or decay and temporal resolution is poor. We established a combination of metabolic labeling of newly transcribed RNA with quantitative separation of labeled and unlabeled cellular RNA. With this new approach we studied the transcriptional response to interferons at a high temporal resolution.

Microarray analyses of both newly transcribed and total cellular RNA provided a comprehensive profile of the temporal order and kinetics of IFN-mediated changes in gene expression. Microarray sensitivity for regulatory changes was increased by >10-fold. Due to higher temporal resolution effects considered so far as primary could now be identified as secondary ones. In fact, more than 25% of IFN-induced changes detectable after 3 h are already marred by secondary signaling events. Employing new computational tools provided highly precise data on RNA decay. We reveal a highly connected network of short-lived transcripts associated with cell cycle and apoptosis which is selectively down-regulated by IFN within 1 h

Due to superior sensitivity and general applicability this procedure should be of interest for a large number of projects in NGFNplus and NGFNtransfer.

Predicting pathway membership via domain signatures

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Motivation: Functional characterization of genes is of great importance, e.g. in microarray studies. Valueable information for this purpose can be obtained from pathway databases, like KEGG. However, only a small fraction of genes is annotated with pathway information up to now. In contrast, information on contained protein domains can be obtained for a significantly higher number of genes, e.g. from the InterPro database.

Results: We present a classification model, which for a specific gene of interest can predict the mapping to a KEGG pathway, based on its domain signature. The classifier makes explicit use of the hierarchical organization of pathways in the KEGG database. Furthermore, we take into account that a specific gene can be mapped to different pathways at the same time. The classification method produces a scoring of all possible mapping positions of the gene in the KEGG hierarchy.

Evaluations of our model, which is a combination of a SVM and ranking perceptron approach, show a high prediction performance. Moreover, for signaling pathways we reveal that it is even possible to forecast accurately the membership to individual pathway components. The complete method is available in the R package *gene2pathway* on the CRAN repository (http://cran.at.r-project.org/).

National Genome Research Network

Oral presentation abstracts

Symposium III

Genome Regulation

Opening Keynote Presentation
Symposium III – Genome Regulation O-3-1

Computational Regulatory Genomics

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In this talk we review a biophysical method for prediction of transcription factor affinity to binding sites on the DNA.
The affinity prediction is calibrated to reproduce ChIP-chip values where these are available, while also allowing for prediction solely based on a weight matrix description of a binding site. Recently, we also computed statistics for the significance of the affinity values, which allows comparing predicted binding behavior of different factors. Further, we computed tissue specific transcription factors by analyzing promoters from sets of tissue specific genes. Results confirm established knowledge and provide several new predictions.

Genome-wide identification of microRNA targets by pulsed stable isotope labelling (pSILAC)

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Animal microRNAs (miRNAs) regulate gene expression by inhibiting translation and/or by inducing degradation of target mRNAs. It is unknown how much translational control is exerted by miRNAs on a genome wide scale. Current methods for system-wide gene expression analysis detect changes in mRNA abundance, but neglect regulation at the level of translation. We developed pulsed stable isotope labeling by amino acids in cell culture (pSILAC) with two heavy isotope labels to directly quantify protein translation on a proteome-wide scale. We used pSILAC to measure changes in synthesis of several thousand proteins in response to miRNA transfection. In parallel, we analyzed mRNA levels by microarrays. We find that a single miRNA can repress production of hundreds of proteins but that this repression is relatively mild. A number of known miRNA binding site features such as the seed sequence also govern repression of protein synthesis and we report additional target sequence characteristics. Our data demonstrate that in addition to down-regulating mRNA levels, miRNAs also directly repress translation of hundreds of genes. Finally, our data also suggests that a miRNA can, by direct or indirect effects, tune protein synthesis from thousands of genes.

Looking at microRNA and mRNA profiles and related epigenetic variations in promoter regions of pancreatic cancer samples

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Pancreatic cancer is the fifth leading cause of cancer deaths in developed countries. In 2002, it was responsible for 227,000 deaths globally, more than for prostate cancer. Histologically, pancreatic cancer is a rather homogeneous tumour: more than 90% are ductal adenocarcinomas, with islet-cell tumors constituting an additional 5%. Currently, there is no effective screening test. Therefore, it is often diagnosed at an advanced stage, contributing to a five-year survival rate of less than 5%.

As part of ongoing activities toward a comprehensive molecular characterisation of pancreatic cancer, comparative studies are under way within the IG Pancreatic Cancer on cancer and normal tissue samples, analysing (i) the epigenetic modulation of the genome, (ii) the effect of sequence variations on transcription factor binding, (iii) genome-wide measurements of transcript levels as well as (iv) the measurements of the actual expression of proteins and (v) their interactions.

Although several transcriptional profiling studies have been performed, we currently pursue a messengerRNA analysis on *Illumina* microarrays with about 1200 samples for an improved characterisation. Some 250 of these samples, including 20 samples that consist of microdissected tumour cells only, are also profiled on microRNA-specific microarrays of *febit biotech*, representing the most recent release of microRNA annotation. Concurrently, epigenetic profiles are produced with the genomic DNA, investigating the methylation statuses of the CpGs in relevant promoter regions.

On this basis, also taking into account SNP data, we aim at the identification of strong associations between molecular pattern variations detectable across different molecular levels and their functional consequences and related disease risk.

Histone demethylase LSD1 is highly expressed in poorly differentiated neuroblastoma and is a novel therapeutic target

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Purpose: The importance of epigenetic gene regulation has been established in neuroblastoma for both DNA methylation and histone acetylation. Histone methylation has long been considered to be irreversible and less versatile. Recently, a new class of histone-modifing enzymes, the histone demethylases, has been identified. These enzymes regulate transcription by specifically demethylating histone residues in promoter regions. Here we address the functional significance of the expression of the lysine-specific histone demethylase 1 (LSD1) in neuroblastoma, and identify LSD1 as a novel therapeutic target.

Methods: LSD1 expression was analysed using Affymetrix microarrays (n=102) and on a neuroblastoma tissue microarray (n=99). The effect of LSD1 knock-down or inhibition was analysed in cell-based assays *in vitro*. Nude mice harbouring neuroblastoma xenografts were treated with a small molecular LSD1 inhibitor.

Results: LSD1 was highly expressed in undifferentiated neuroblastomas, while LSD1 levels were reduced in differentiating neuroblastomas and ganglioneuromas. Kaplan-Meier analysis revealed high LSD1 expression to be correlated with adverse outcome. Inducing neuroblastoma cell differentiation *in vitro* with all-trans retinoic acid resulted in significant downregulation of LSD1 expression. Knock-down of LSD1 with siRNA led to decreased cellular viability and the induction of differentiation-associated gene expression patterns. Inhibition of LSD1 with the FDA-approved monoamine oxidase inhibitors, pargyline, clorgyline and tranylcypromine, in neuroblastoma cell lines resulted in an increase of global H3K4 dimethylation and cell death. Treatment of nude mice with tranylcypromine reduced xenograft size *in vivo*.

Conclusions: This suggests that LSD1-mediated histone de-dimethylation might be involved in transcriptional silencing of differention and/or apoptotic programmes inherent in neuroblastoma cells. This makes LSD1 a bona fide target for therapeutic intervention.

Predicting DNA-binding specificities of transcription factors

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Despite a large effort to unravel DNA-binding specificities of Transcription Factors (TFs), to date they are known only for a small fraction of TFs. To increase this coverage Suzuki and Yagi presented one of the first methods to predict DNA-binding specificities for TFs, by deriving a fixed number of chemical rules from 25 protein crystal structures. Following this initial publication, other works have been applied to specific subclasses of TFs or certain species, such as E. coli.

To devise a more general method, in this work, an approach is presented that allows for predicting DNA-binding specificities from annotated protein sequences of TFs. At its core this method compares protein sequences of TFs, and from these predicts how similar their DNA-binding specificities are - modeled as Position Frequency Matrices (PFMs). Based on this information PFMs can be transferred between TFs within and across species. Thus, PFMs are not directly predicted from the protein sequence of the query protein, but transferred and merged between TFs. To obtain such a model a SVR is trained with a local distance metric learning approach, on a dataset covering 1,239 TFs with known PFM. This training set allows to generate robust models and calculate the statistical prediction error. This method is subsequently applied to 3,636 TFs with unknown PFMs, thereby predicting the DNA-binding specificity of 438 TFs with high accuracy.

National Genome Research Network

Oral presentation abstracts

Symposium IV

Animal, Cellular & Tissue Models

Opening Keynote Presentation
Symposium IV – Animal, Cellular & Tissue Models O-4-1

The Role of Transgenic Rats in a Genome Wide Association Studies (GWAS) World

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A 2008, animal models are selected primarily on one of two criteria: 1.) a gene or its expression is modified or can be modified and its implication in a human disease can be studied in a particular model system; 2.) the physiological characteristics of the model systems reflect some aspect of the clinical picture. There has been some movement towards other considerations such as genome background and effects of the environment (e.g. diet). However, it appears that the added benefit of comparative genomics is seldom considered when a model is selected. With a large number of quantitative trait loci (QTL) genetically mapped in many different species, and many mapping to the same evolutionarily conserved regions, it seems reasonable that many of the same genes will play a role in the same disease process.

For many years the role of animal systems in genetic studies has been predicated on the increased heritability, flexibility and statistical power of experimental crosses over corresponding studies in humans. The new human genome wide association studies (GWAS) and re-sequencing programs are now able to sift the genome of the human without the need of animal model data, therefore raising a question concerning the continuing value of animal genetics studies. As the results of human GWAS continue to reveal the genetic basis of common human diseases in spectacular fashion, the need for a multi-species platform, to integrate and investigate human disease at the level of both genotype and phenotype has become increasingly apparent. The molecular mechanisms underlying these associations are frequently unclear even once statistically robust and replicated associations have been demonstrated. Because of the small gene effects and tight linkage disequilibrium between markers, dissecting many of these genetic associations by further studies in humans may be difficult or impossible. The rat with corresponding transgenesis and systems biology offer the ability to unravel the genes and their mechanisms of action of genes responsible for common complex diseases.

As the rat remains the dominant rodent system for preclinical studies within the pharmaceutical industry, transgenic rats have the potential to significantly influence drug development. The ability to generate gene modifications, particularly with respect to drug metabolizing enzymes would be of high value. At the Medical College of Wisconsin and PhysioGenix we have used classical genetics to build better rat models. The prospects of new types of transgenic rats in this context will be discussed.

IG-CSG- cellular systems genomics

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Building on expertise, research tools, technologies, capacities and collaborations established in NGFN-2 (e.g. within SMP-Cell), IG Cellular Systems Genomics generates knowledge on fundamental molecular, cellular, and disease-relevant processes. Our main objectives are:

- to apply qualitative and quantitative functional genomic, proteomic, and cell biological strategies, in order to analyse the dynamics and cross-talk of signalling pathways and networks *in vitro* and *in vivo*.
- to generate systems genomics models that predict and validate novel markers for diagnosis and prognosis as well as target molecules with potential for therapeutic intervention.
- to apply and validate the gained knowledge in breast cancer, where drug resistance mechanisms shall be elucidated. Here we aim to define routes that shall prevent acquired drug resistance and lead to tumour remission.

For more information, please visit http://www.igcsg.org

Identification of new targets playing a role in metabolic diseases by systemic analysis in the German Mouse Clinic

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We have established the German Mouse Clinic (GMC) for systemic phenotyping of mutant mouse lines to model genetic human diseases. Ás of May 2008, 84 mutant lines (predominantly from members of the NGFN) have been analyzed in the primary screen of the GMC (320 key parameters in 14 different disease areas). In 95 % of the lines, new or additional phenotypes have been identified.The Mouse Clinic concept enables us to study the pleiotropic effects of gene-environment-interactions and the systemic features of complex diseases like obesity and diabetes. Major health problems are caused by disturbances in energy balance due to the dysfunctional regulation of energy intake or expenditure. Long term maintenance of a positive energy balance results in the development of obesity, which is associated with the metabolic syndrome. As the prevalence of obesity is constantly increasing, it is identified as a prime public health risk factor.

New animal disease models are in the centre of interest to identify previously unknown genes related to energy balance regulation. With a special focus on phenotypes related to dysfunctional body mass regulation, the Energy Metabolism Screen at the GMC successfully identified 8 mutant lines with increased body mass and 30 underweight mutant mouse lines. A broad phenotypic characterization of the over- and underweight mutants could help to establish new animal models for disturbed energy homeostasis regulation and to elucidate novel pathways involved in the pathogenesis of metabolic diseases. We are currently including genotype-environment-interactions in the analysis of mutant lines and will switch from a constant to a variable environment by establishing "environmental platforms" such as the Nutrition Platform with routinely implemented dietary challenge experiments (e.g. cafeteria diet).

Modulation of neuropathic pain by endocannabinoids

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Introduction: Neuropathic pain develops as a consequence of peripheral nerve injury or degeneration. Because it is difficult to treat even with potent analgesic drugs there is a great medical need for novel pharmacotherapies. Recent studies suggest that CB2 selective ligands may fill that need, as they seem to be effective in animal models of neuropathic pain. In this study, we have investigated CB2 mediated mechanisms in the modulation of neuropathic pain.

Methods: We used genetically modified mice lacking or overexpressing cannabinoid CB2 receptors to evaluate the contribution of these receptors in the development of neuropathic pain. We performed partial sciatic nerve ligation followed by nocicepive, histological and expression profiling studies. INF-□ and CB2 receptor double knockout mice, as well as irradiated wild type mice receiving bone marrow transplantation from CB2 knockout animals were used to address the role of inflammatory responses.

Results: CB2 knockout animals subjected to a partial nerve injury developed mechanical allodynia and thermal hyperalgesia to a similar extend as wild type control animals on the ipsilateral side of the nerve injury. However, unlike wild type mice, they also displayed increased pain sensitivity on the contralateral side. In contrast, transgenic mice overexpressing CB2 receptors had attenuated neuropathic pain responses. Expression profiling studies revealed an enhanced INF-□ response in the absence of CB2 receptors. Analysis of double knockout animals confirmed that the enhanced INF-□ response caused the expansion of the hyperalgesic area in the absence of CB2 receptors.

Discussion: These results suggest that CB2 mediated mechanisms contribute to the local containment of the hyperalgesic response after peripheral nerve injury. CB2 receptors thus represent an interesting therapeutic target for the treatment of neuropathic pain.

Myosin light chain-1 controls cardiac contractility

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Despite the fact that myosin light chains are major constituents of thick filaments of heart and skeletal muscle cells, surprisingly little is know about their structural and especially their functional roles in the vertebrate heart. By isolation of the zebrafish mutant *tell tale heart*, we recently successfully elucidated in detail how regulatory cardiac myosin light chains contribute to heart contractility and when defective, might induce human cardiomyopathies.
In a succeeding screen for ENU-induced zebrafish mutants with affection of cardiac contractility, we isolated the recessive-lethal mutation *laz.* By a posititional cloning approach we identified a point-mutation within the cardiac essential myosin light chain-1 gene, which predictably leads to premature stop of cMLC-1 protein translation. Whereas complete loss of cMLC-1 leads to cardiac acontractility due to impaired cardiac sarcomerogenesis, expression of mutated cMLC-1 in *laz* mutant hearts is sufficient for normal cardiac sarcomerogenesis but severely impairs cardiac contractility in a cell-autonomous fashion.Our data reveal for the first time a functional role of cMLC-1 in regulating cardiac contractility *in vivo* in the vertebrate heart. Hence, in future studies it will be interesting to further dissect the impact of cMLC-1 mutations in human heart diseases and to evaluate if targeted modification of cMLC-1 might be a new therapeutic approach to human cardiomyopathies and heart failure.

National Genome Research Network

Oral presentation abstracts

Symposium V

Genomic / Environmental Interaction

From genome wide association studies to risk prediction: the importance of studies of gene interactions.

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In recent years, there have been major successes in the identification of new genetic variants involved in complex genetic disorders. Although replicated, most of these new variants show extremely small effects on disease risks, explaining only a minor part of the heritability of disease. Even combined in genetic risk profiles, the new genetic variants identified have a limited contribution to the prediction of disease over classical risk factors of disease such as obesity. This modest contribution does not match with the high recurrence risks of disorders in families. This paradox may in part be explained by the existence of unrecognized gene-interactions. One of the major challenges for the next decades will be to unravel the interactions between genetic variants and environmental factors. The prospects of genome wide environment studies will be discussed from an empirical and methodological perspective. From a theoretical perspective, studies of gene interactions follow the standard genome wide association approach. However, assessing the effect of environmental factors raises important questions on the validity of retrospective exposure assessment, asking for large prospective studies with long term follow-up. Other major practical barriers to cross concern the statistical power dictating large sample sizes in the gene-interaction discovery phase and the need for replication samples of even larger size to exclude false positive findings. Last but not least, a crucial issue to resolve concerns the definition of interaction from a statistical perspective.

Genetics meets metabolomics: a genome-wide association study of metabolite profiles in human serum

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Background: The rapidly evolving field of metabolomics aims at a comprehensive measurement of ideally all endogenous metabolites in a cell or body fluid. It thereby provides a functional readout of the physiological state of the human body. Genetic variants that associate with changes in the homeostasis of key lipids, carbohydrates or amino acids are not only expected to display much larger effect sizes due to their direct involvement in metabolite conversion modification, but should also provide access to the biochemical context of such variations, in particular when enzyme coding genes are concerned.

Results: To test this hypothesis we conducted the first GWA study with metabolomics, based on the quantitative measurement of 363 metabolites in serum of 284 male participants of the KORA study. We found associations of frequent SNPs with considerable differences in the metabolic homeostasis of the human body, explaining up to 12% of the observed variance. Using ratios of certain metabolite concentrations as a proxy for enzymatic activity, up to 28% of the variance can be explained (p-values 10^{-16} to 10^{-21}). We identified four genetic variants in genes coding for enzymes (FADS1, LIPC, SCAD, MCAD) where the corresponding metabolic phenotype (metabotype) clearly matches the biochemical pathways in which these enzymes are active.

Conclusions: Our results suggest that common genetic polymorphisms induce major differentiations in the metabolic make-up of the human population. This may lead to a novel approach to personalized health care based on a combination of genotyping and metabolic characterization. These genetically determined metabotypes may subscribe the risk for a certain medical phenotype, the response to a given drug treatment, or the reaction to a nutritional intervention or environmental challenge.

Reference: Gieger C et al., Genetics meets metabolomics: a genome-wide association study of metabolite profiles in human serum. Plos Genetics to appear.

Response to ultrafine particle instillation in two mouse strains with extremely divergent lung function

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Background: In search for strain-specific phenotype variance of lung function parameters among common mouse inbred strains we identified the strains C3H/HeJ (C3) and JF1/Msf (JF1) to represent the two most divergent strains; with JF1 being eye catching for its limited lung size parameters. A subsequent genome-wide linkage analysis within mice from respective crossings detected several quantitative trait loci (QTLs) associated to lung size. Some of the QTL underlying candidate genes like extracellular superoxide dismutase (SOD3) suggest a possible causal link between the antioxidant pathway and mechanisms of lung development or function. Since oxidative stress is apart from its lung function effects known as an important mediator for acute toxicity of oxidizing air pollutants like ultrafine particles (UfP), we aimed to compare the susceptibility of C3 and JF1 mice to UfP induced lung injury.
Methods: Mice of both strains were comparatively exposed by intratracheal instillation with 5, 20 and 50 µg of carbonaceous UfP (Printex90) and investigate for the pulmonary response after 1, 3 and 7 days.
Results: In view of the influx of inflammatory cells in to the lungs 24h after instillation, C3 mice show a regular dose response, whereas for JF1 mice granulo- and lymphocyte numbers where highest at the intermediated particle dose. Accordantly 7 days after 20µg instillation in C3 lungs inflammatory cells numbers (granulo- and lymphocytes) dropped back to baseline, whereas in JF1 lungs at this time point lymphocte numbers were still increasing.
Conclusions: Our data suggests that molecular pathways contributing to antioxidant balance are involved in both: (i) lung development and (ii) inflammation, respectively its resolution. This hypothesis might explain, why air pollutants not only affect lung function parameters via inflammatory pathways, but also why individuals with reduced lung function are more susceptible to oxidizing air pollution.

Alcoholism – A Systems approach from molecular physiology to addictive behaviour

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Alcohol consumption is an integral part of daily life in many societies. The benefits associated with the production, sale and use of alcoholic beverages come at an enormous cost to these societies. The World Health Organization ranks alcohol as one of the primary causes of the global burden of disease in industrialized countries. Alcohol-related diseases, especially alcoholism, are the result of cumulative responses to alcohol exposure, the genetic make-up of an individual and the environmental perturbations over time. This complex gene x environment interaction, which has to be seen in a life-span perspective, leads to a large heterogeneity among alcohol-dependent patients, in terms of both the symptom dimensions and the severity of this disorder. Therefore, a reductionist approach is not very practical if a better understanding of the pathological processes leading to an addictive behaviour is to be achieved. Instead, a systems-oriented perspective in which the interactions and dynamics of all endogenous and environmental factors involved are centrally integrated, will lead to further progress in alcohol research. This review adheres to a systems biology perspective such that the interaction of alcohol with primary and secondary targets within the brain is described in relationship to the behavioural consequences. As a result of the interaction of alcohol with these targets, alterations in gene expression and synaptic plasticity take place that lead to long-lasting alteration in neuronal network activity. As a subsequent consequence, alcohol-seeking responses ensue that can finally lead via complex environmental interactions to an addictive behaviour.

Tbc1d1 mutation confers leanness and protects from diet-induced obesity and diabetes

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In genome-wide scans of outcross populations of the New Zealand obese (NZO) mouse and the lean SJL strain we have previously identified a major QTL for high-fat diet (HFD)-induced obesity and diabetes (*Nob1*; LOD score 7.9) on chromosome 5. Additional crossbreeding experiments indicate that *Nob1* represents an obesity suppressor from the SJL strain. We here identify a SJL-specific 7 bp deletion in the *Tbc1d1* gene which results in a truncated protein lacking the TBC/Rab-GTPase activating (GAP) domain. Introgression of the *Nob1* segment of the SJL chromosome 5 into a mixed NZO/C57BL/6J background markedly reduces body weight and blood glucose levels. TBC1D1 which has been recently linked to human obesity, is related to the insulin signalling protein AS160, and is predominantly expressed in skeletal muscle. Knockdown of TBC1D1 in skeletal muscle cells increases fatty acid uptake and oxidation whereas overexpression of TBC1D1 has the opposite effect. Recombinant congenic mice lacking TBC1D1 show a decreased respiratory quotient, increased fatty acid oxidation and reduced glucose uptake in isolated skeletal muscle. Our data strongly suggest that mutation of *Tbc1d1* suppresses high-fat diet-induced obesity by increasing lipid use in skeletal muscle. Thus, TBC1D1 might be involved in a novel pathway that regulates energy homeostasis in both mice and humans.

National Genome Research Network

Oral presentation abstracts

Symposium VI

Transfer from Genomics to Application

Opening Keynote Presentation
Symposium VI – Transfer from Genomics to Application O-6-1

Bert Klebl

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From Genomes to Drugs

… is a very long and rocky way. Starting with a first hypothesis, it usually takes more than 15 years to come up with a new drug candidate. The first part is intense in research, a process by and large underestimated in the academic community. Provided that the genomics era started in the late '90s, we do not seriously expect genomics-based drugs on the market today. We are still in the applied research phase, in the process of translating genomics results into therapeutic applications. Here, three short case studies are presented: 1, the Herceptin case demonstrates how an efficient transfer into clinical application can look like; 2, PknG is a mycobacterial kinase target, identified by means of comparative genomics. Inhibitors thereof might be useful in the treatment of latent tuberculosis; 3, cyclinT1 is up-regulated in activated T cells and in macrophage differentiation. CyclinT1 is a co-factor of CDK9, a kinase regulating transcription. Inhibitors thereof might be useful in the treatment of HIV and inflammatory diseases.

The case stories underscore the importance of identifying modulators of potentially novel targets early on. Chemical probes become ever more important in dissecting genomic results. Therefore a paradigm shift in drug discovery is necessary, trying to avoid laborious target validation periods and rather starting chemical validation of pathophysiological processes as early as possible. That is exemplified by the more recent initiatives of establishing screening and drug discovery centers at or in vicinity to academic research institutes.

Defining PI3-Kinase dependency in non-small cell lung cancer

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MLS and SF contribute equally to this work.The PI3-Kinase plays a critical role in oncogenic signalling in cancer. In order to determine which genetic alterations in non-small-cell lung cancer (NSCLC) might be associated with oncogene dependency on PI3-Kinase signalling, we performed a high-throughput chemical genomics screen using a library of PI3-Kinase inhibitors. Using a large, genomically and phenotypically annotated lung cancer cell line panel we screened this library. We used a variety of phenotypic assays as readouts and linked pharmacological data to genomic data employing various computational approaches. Finally, structural modelling and chemical genetics experiments were performed to validate cells, which display exquisite dependency on PI3-Kinase signalling. We find that PI3-Kinase inhibition induced growth arrest at nanomolar concentrations in over 60% of the cell lines. Furthermore, in 20% of the cell lines, PI3-Kinase inhibition resulted in a significant induction of apoptosis suggesting a particular dependency on this pathway. We identified p110-alpha as the relevant target of PI3-Kinase inhibition by profiling of isoform-selective inhibitors and validated this observation by expressing drug-resistance alleles in sensitive cells, which abolished the phenotype. Finally, computational prediction of phenotypes using genomic lesion data yielded molecular predictors of sensitivity to PI3-Kinase inhibition. Our results suggest that PI3-Kinase inhibition is an effective therapeutic strategy in NSCLC. More broadly, high-throughput chemical genomics profiling involving genomically annotated cancer cell line panels offers a rich source for preclinical target identification and estimation of therapeutic efficacy prior to clinical trials.

Functional impact of polymorphisms on the human delta-6 desaturase gene promoter

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Fatty acid desaturases play an important role in the formation of omega-6 and omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs). The composition of LC-PUFAs in the human body is important for the modulation of essential physiological functions like inflammation processes and brain development. The effect of single nucleotide polymorphisms (SNPs) in the human FADS gene cluster on LC-PUFA levels and composition has been investigated recently in several different studies. All reported significant associations with several SNPs, with a decrease of desaturase reaction products and an accumulation of substrates when the minor allele was present. This observation suggests a decline in the transcriptional levels or in the conversion rates of the desaturases due to the polymorphisms. We performed functional studies with two of the associated polymorphisms (rs3834458 and rs968567) located in the delta-6 desaturase (*FADS2)* gene promoter and showed an influence of both polymorphisms on delta-6 desaturase promoter activity demonstrated by luciferase reporter gene assays in three different cell lines. Furthermore, electrophoretic mobility shift assays proved allele-dependent DNA-binding ability of at least two proteins or protein complexes to the region containing the SNP rs968567. These results show for the first time that the investigated polymorphisms have an influence on the delta-6 desaturase promoter activity and offer first insights into the modulation of complex regulation mechanisms of desaturase gene transcription by SNPs.

Xenogeneic Immunization with Human Tyrosine Hydroxylase DNA Vaccines Effectively Eradicates Established Neuroblastoma and Induces Long Lasting Protective Immunity

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Introduction: DNA vaccination against cancer antigens is considered to induce weak anti-tumor immune responses in humans. In order to enhance vaccine efficacy, xenogeneic immunization is a promising approach, in particular for neuroblastoma. Neuroblastoma cells highly express the enzyme tyrosine hydroxylase (TH). Previous prophylactic vaccinations with human TH (hTH) DNA vaccines induced an effective CTL-mediated anti-neuroblastoma immune response in mice. Here, we report its efficacy in a therapeutic vaccination setting.

Methods: hTH cDNA was cloned into mammalian expression vector pCMV-F3Ub. A/J mice were challenged subcutaneously (s.c.) with a lethal dosage of syngeneic NXS2 neuroblastoma cells (day 0). Therapeutic vaccination was carried out on day 3 and 8 after tumor cell inoculation by oral gavage of attenuated *Salmonella typhimurium* SL7207 bearing the hTH cDNA and empty vector controls. Primary tumor growth rate was monitored over time until tumor sizes reached a volume greater than 500mm^3. At that time, primary tumors were removed surgically and mice received a third immunization 14 days post surgery. Survival of mice was determined over time. Mice surviving longer than 90 days after tumor cell injection were re-challenged with a lethal dosage of wildtype NXS2 cells.

Results: Therapeutic vaccination with hTH cDNA induced long term survival in 50% of mice for up to 90 days. In 50% of the hTH cDNA vaccinated mice, established tumors were eradicated following first and second vaccination. Importantly, after re-challenge, tumor growth was suppressed in the hTH cDNA survivor mice compared to the naïve control group.

Conclusion: In summary, we report that an hTH cDNA vaccine effectively eradicates established s.c. tumors in mice, significantly prolongs their survival and suppresses tumor growth after a lethal re-challenge. Therefore, we think that xenogeneic vaccination with TH DNA vaccines is a promising concept for active immunotherapy in neuroblastoma.

High-throughput sequencing of snap frozen and paraffin embedded cancer and normal tissues

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Up to now cancer sequencing programs relied on DNA isolated from fresh frozen tissues, access to which is a major bottle neck. The use of preserved material, i.e. from tissue banks, could help to avoid this limitation and would enable the reanalysis of diverse clinical trials. So far we have shown that formalin-fixed paraffin-embedded (FFPE) tissue samples can be used for genomic re-sequencing processes. FFPE samples are amply available from surgical tumor resections and histopathological diagnosis, and comprise tissue from precursor lesions, primary tumors, lymphogenic and/or hematogenic metastases. To generate models which predict the response to therapy, FFPE tissue has also the advantage that it is available from a variety of clinical trials. In addition to the applicability of second generation sequencing techniques to snap frozen and FFPE tissues we present data on the detection of copy number variations in breast cancer tissues.

In order to enable a cost efficient re-sequencing of more than 50.000 exons we are using a sequence-specific enrichment of DNA for which we are now trying to set up an automation pipeline. In addition we have already successfully sequenced the non-coding RNA pools including the miRNA content of several tumor samples which is of particular interest for the characterisation of tumor - stages and - progression.

Taken together, modern high-throughput sequencing techniques in combination with novel protocols for the extraction and quality monitoring of nucleic acids from FFPE tissue offer the possibility to obtain an overall image of the molecular changes in cancer as a prerequisite for computational modelling.

Evening Lecturer

High resolution proteomics in functional genomics

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In-depth quantitative proteomics – For the last 30 years, a 'holy grail' of proteomics has been the quantitation of entire proteomes. Here we report that this is now possible for simple systems such as yeast. Furthermore, mammalian systems can be probed by proteomics to equivalent depth as in microarray technology. Key advances required to achieve this systems-wide quantitation were the development of novel algorithms that dramatically increased peptide mass measurement accuracy and well as the proportion of identified peptides. With this technology, we can now measure protein abundance changes for the entire proteome and as a function of arbitrary perturbations.

Quantifying phosphoproteome and proteome for systems biology – Using the SILAC technology combined with high resolution mass spectrometry, it is now possible to quantify both phosphoproteome and proteome changes at a systems wide level following any 'signal'. Examples of cytokine stimulation in different cell types will be given. The phosphoproteome typically yields the early stages of 'information processing' in the cell, whereas the proteome changes reflect the ultimate outcomes at the functional level. It is in principle possible to add measurement of epigenetic state, mRNA changes, microRNA changes as well. Thus we now have the tools to follow a stimulus or developmental program through a hierarchy of five distinct biological levels of control.

Strategies for application to human subjects – The above examples were mainly restricted to work in cell culture. For the mouse model, we have recently shown that SILAC-whole animal labeling is feasible and allows studying any tissue of choice (Krueger et al, Cell, 2008). For human subjects, we propose two strategies. The first involves SILAC-labeling one or more cell lines that correspond to the tissue of interest. These labeled cells are then mixed with case and control to derive a quantitative proteome. The second involves novel algorithms for 'label free quantitation', in which the MS signal of each peptide is compared across a number of patients. Our data indicates that this technology is less accurate than SILAC but appears to be at least as accurate as the more familiar microarray technology.

National Genome Research Network

Poster presentation abstracts

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Poster presentation abstracts

Symposium I

Genomics of Common Disease

Global analyses of molecular differentiation pathways in brain-tumor stem cells

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The concept of cancer as a disease that typically originates in the stem and progenitor cell population suggests that differentiation therapy will be a viable approach for cancer therapy. This has been supported by the successful clinical application of differentiating agents such as retinoic acid in clinical settings. We established and characterized primary cultures that are enriched in CD133-positive tumor-initiating cells from 20 glioblastoma. Putative glioma-pathogenesis relevant genes were identified and gene expression and DNA-copy number status compared to data from about 100 primary tumors. Upon exposure to retinoic acid, the tumor-initiating cell cultures altered their growth patterns, from spheroidal to various degrees of adherent growth. These morphologic changes are accompanied by a significant drop of tumorigenicity and invasiveness in the NOD-SCID-xenograft model. Genetic and epigenetic analyses of cells before and after treatment with retinoic acid revealed effects on gene expression of, among others, WNT, IGF and TGF inhibitors, and on the expression of oncogenic miRNA clusters that might directly regulate tumor invasiveness and angiogenic potential.

Identification of oncomirs targeting feedback regulators of EGFR signalling

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Negative feedback mechanisms play a key role in the attenuation of mitogenic epidermal growth factor receptor (EGFR) signaling, deregulation of which leads to prolonged receptor signaling and thus uncontrolled proliferation of cells. Recently, several regulatory feedback components have been identified including MIG6, LRIG1 and c-CBL. MIG6 expression is induced in response to EGFR activation and it in turn inhibits EGFR. LRIG1 is a transmembrane protein that is upregulated upon EGF stimulation and enhances ubiquitinylation of the activated receptor by the ubiquitin ligase c-CBL. MicroRNAs are small non-coding RNAs regulating post-transcriptional gene expression by translational repression or mRNA degradation. Recently, it was shown that miRNAs can work in concert with RNA binding proteins e.g.ZFP-36 -regulators of the EGFR signaling- giving a hint for their role in the feedback regulation.

Here we aimed at identifying miRNAs which repress the expression of these feedback regulators and thus lead to increased signaling. We first predicted candidate miRNAs which might target the 3' UTR of each of these individual genes using six different target prediction algorithms. The stringency of the selection was increased by filtering for miRNAs which are predicted in at least three of the prediction databases and choosing the miRNAs which inhibit the genes that share the same functional domains (GO terms) with the three regulatory proteins. In the characterized cell systems, effects of the miRNAs on the expression of MIG6, LRIG1 and c-CBL and also on the transient and sustained activation of the pathways will be investigated using miRNA mimics and inhibitors. The potential candidate miRNAs will be exploited in dual-luciferase assay to determine their direct targeting of the feedback regulator proteins. Finally, identified miRNAs will be examined in cancer-related assays and also in patient samples to determine their oncomir functions.

A novel large-scale screen to identify modulators of miR-21

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MicroRNAs (miRNAs), endogenous small non-protein-coding RNAs, are primary regulators of differential gene expression in many basic cellular processes including proliferation, differentiation and apoptosis. Recent evidence has shown that alterations in miRNA expression can also contribute to tumor growth by modulating critical genes. MiR-21 is upregulated in breast cancer, prostate cancer, glioblastoma and other cancers and has been proven also to correlate with tumor stage.

To identify genes involved in the regulation of miR-21 we are screening a siRNA-library of 4400 selected siRNAs, chosen based on their potential to regulate microRNA biogenesis. For a primary screen, four target sites for miR-21 have been cloned into the 3'-UTR of a luciferase reporter-gene. In this way, changes in miR-21 level after transfection of siRNAs result in changes of luciferase concentration. The feasibility of this system was proven by knocking down known genes involved in microRNA-biogenesis as positive controls. Currently, we are in the process of carrying out this screen. Hits in the primary screen will then be validated by a secondary screen, which detects changes in miR-21 concentration directly by using quantitative real time PCR. Thus, by these screens we aim to identify novel tumor-promoting or tumor-suppressing genes, which modulate tumor growth by regulating miRNAs.

The alteration of miR-21 expression by modulating expression of the identified genes might change tumor development. Therefore, these genes may also serve as therapeutic targets. Moreover, these genes will also be analyzed for their ability to regulate other miRs to potentially identify general mechanisms of miR-regulation.

Case-control study of genetic susceptibility in early onset lung cancer: Investigation of Matrix Metalloproteinase 1 (MMP1)

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It is assumed that a combination of smoking and genetic components leads to greater susceptibility to lung cancer especially within early onset of disease. Matrix Metalloproteinases (MMPs) play a key role in the breakdown of extracellular matrix and in inflammatory processes. MMP1 is the most highly expressed interstitial collagenase degrading fibrillar collagens. 635 young cases (age below 51) were recruited nationwide. These were compared to 1300 cancer free controls. Cases and controls were frequency matched by age and sex. Genotype information of MMP1 was obtained for 11 SNPs. Conditional logistic regression analysis was used to calculate odds ratios (OR) for risk of early onset lung cancer associated with each SNP and for LD sets in haplotype analysis. Two regions of linkage equilibrium (LD) within MMP1 could be observed: a region of low LD covering the 5' region including the promoter and a region of high LD starting from exon1 to the end of the gene and including the 3' flanking region. Three adjacent SNPs (rs1938901, rs193008 and rs996999) in the region of higher LD were identified to be significantly associated with risk of early onset lung cancer. For rs1938901 an increase in the risk for lung cancer was estimated for heterozygotes (CT) (OR = 1.5, 95%CI: 1.0-2.2, p = 0.0534) and for homozygotes (CC) (OR = 1.8, 95% CI: 1.2 - 2.7, p = 0.0033). Rs1938901, which is in high LD with rs193008, showed an almost identically increased lung cancer risk for carriers of the G allele. A significant association with higher risk of lung cancer for carriers of the C allele was also observed for rs996999, with an OR = 1.3 (95%CI: 1.0 - 1.5, p = 0.0152) for each allele, but significance of this SNP vanished after correction for multiple testing. Using haplotype analysis we could narrow the region containing the disease relevant DNA-variant. In summary, we identified MMP1 to be associated with an increased risk for lung.

New genetic evidence for involvement of the dopamine system in migraine with aura

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In order to systematically test the hypothesis that genetic variation in the dopamine system contributes to the susceptibility to migraine with aura (MA), we performed a comprehensive genetic association study of altogether 10 genes from the dopaminergic system in a large German migraine with aura case-control sample. Based on the genotyping results of 53 variants across the ten genes in 270 MA cases and 272 controls, three genes - DBH, DRD2 and SLC6A3 - were chosen to proceed to additional genotyping of 380 MA cases and 378 controls. Four of the 26 genotyped polymorphisms in these three genes displayed nominally significant allelic P-values in the sample of 650 MA patients and 650 controls. Three of these SNPs (rs2097629 in DBH [uncorrected allelic P-value = 0.0012, OR = 0.77], rs7131056 in DRD2 [uncorrected allelic P-value = 0.0018, OR = 1.28] and rs40184 in SLC6A3 [uncorrected allelic P-value = 0.0082, OR = 0.81]) remained significant after gene-wide correction for multiple testing by permutation analysis. Further consideration of publicly available genotype data from 2937 British control individuals did not affirm the association with DRD2, but supported the associations with DBH and SLC6A3. Our data provide new evidence for an involvement of components of the dopaminergic system - in particular the dopamine-beta hydroxylase and dopamine transporter genes - to the pathogenesis of migraine with aura. Currently hypothesis-free genome-wide association studies for MA are under way, namely in the framework of EMINet and in the context of an international consortium. Since our analysis of the dopamine system was based on haplotype-tagging SNPs, a joint analysis of this dataset with the results obtained in the course of the GWA studies will be possible.

A trafficking defective KV7.2 mutation causing neonatal seizures

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Benign familial neonatal seizures (BFNS) are caused by mutations within the KCNQ2 and KCNQ3 genes encoding voltage-gated potassium channels KV7.2 and KV7.3, which are important regulators of neuronal excitability. BFNS mutations cause a loss-of-function of these channels resulting in an increased neuronal firing. We examined here a BFNS mutation N258S located in S5-H5 linker of the KV7.2 channel. When expressed alone in Xenopus oocytes or CHO cells, the N258S mutation revealed barely measurable currents and its coexpession with KV7.3 yielded currents reduced by 80%, compared to WT KV7.2/KV7.3 coexpression. Single channel recordings did not reveal changes in single channel conductance or open probability suggesting that the observed reduction in current is due to a reduced number of channels in the surface membrane. To verify whether the N258S mutation causes a trafficking defect, we incubated cells expressing WT or mutant KV7.2 channels either at < 30oC or with a specific channel opener Retigabine prior to whole cell measurements. The observed temperature and pharmacological rescue (N258S currents were 5-fold increased) strongly indicates that a mechanism by which the N258S reduces K+-currents is either a misfolding or trafficking deficiency of the affected channel proteins. In the next step we examined primary neurons obtained from embryos of KCNQ2 knock-out mice. The characterization of +/- and -/- primary hippocampal neurons revealed reduced M-current amplitudes and increased neuronal firing. The -/- neurons could be used as an expression system free of endogenous KV7.2 channels to examine effects of BFNS mutations in natural neuronal environment.

From Disease Genes to Protein Pathways: the DIGTOP project

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Progress in human genetics has identified mutants in numerous genes that are linked with disease but does not place them into pathways. It has been difficult, especially for novel genes, to determine how mutations cause disease. Proteomic mapping offers a way forward because it identifies physical relationships and indicates pathways, which can be validated by functional analysis. This map can then serve as the scaffold for understanding transient and regulated interactions. Recent technical advances made it possible to reliably map interactions within the mammalian proteome. Within the DIGTOP project we develop standardized methodology to place disease genes into pathways, using recent advances in genomics and proteomics. For chosen proteins we will knockIn a GFP Tag into the genome of murine ES cells or introduce an engineered BAC transgene into HeLa or human ES cells. The Tag allows to document the subcellular localization of proteins in living ES cells, specialised cell types obtained by in vitro differentation and mice, and to determine their interaction partners by mass spectrometry. Proteins identified as interactors with the tagged protein become candidates for tagging in the next round. This approach, complemented by validation and functional studies, will establish a mammalian proteomic database relevant to disease pathways of unrivalled quality, and a pipeline for study of novel disease genes as they are discovered. The project begins by focusing on 80 genes relevant to Neuropsychiatric conditions, Diabetes, Leukemia, Obesity, Cancer and Alzheimer`s disease.

ProDGe - a sequence and protein interaction viewer

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Alternative splicing and deranged protein-protein interactions constitute one major cause for diseases like Parkinson. A multitude of on-line databases contains data of proteins and their interactions, e. g., UniProt, IntAct, BIND, or provide information about the underlying genes, e. g., NCBI (RefGene), Ensemble or UCSC. Since most databases provide complementing information an integration of all data and visualization are desirable. Here we present ProDGe (Protein Domain Gene), a new program to view domain-domain interactions on protein level and corresponding genetic context. ProDGe is entirely written in Java and consists of two parts: First, Interaction Viewer grants access to proteins with their sequence, gene name and description together with their interaction partners highlighting domain-domain interactions. Predicted and experimentally validated domain-specific protein-protein interactions are made explicit. Second, Sequence Viewer is a full genome browser which visualizes the associated gene sequences with their various annotations. ProDGe uses a MySQL database containing the following data:

(i) protein information from UniProt,

(ii) mapping of domains to their containing protein comes from SwissPfam,

(iii) DOMINE delivers domain information and domain-domain interactions,

(iv) SNPs provided by dbSNP (NCBI),

(v) UCSC yields promoter regions,

(vi) introns, exons and alternative splice forms are taken from ASD and

(vii) miRNA targets from the Wellcome Trust Sanger Institut (WTSI).

The integration of complementing data from various sources and the combination of two viewers into one program allows the user to browse gene information together with resulting proteins and their domain-specific interaction networks. Currently, our database contains 70,668 human proteins, 8,957 domains, 8,884 protein-protein and 20,513 domain-domain-interactions and about 27,212 human genes.

The Parkinson disease-associated protein kinase LRRK2 shares sequence homology with MAP3K and phosphorylates classical MAP3K targets, in vitro

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Autosomal dominant mutations in the human Leucine Rich Repeat Kinase 2 (LRRK2) gene represent the most common monogenetic cause of Parkinson disease (PD). Increased kinase activity observed in pathogenic mutants of LRRK2 is most likely causative for PD-associated neurotoxicity. The sequence of the LRRK2 kinase domain shows similarity to MAP kinase kinase kinases. The highest homology is observed with mixed linage kinases (MLKs) which act upstream of canonical MAPKK and are involved in cellular stress responses. Therefore, we addressed the question if LRRK2 exhibits MAPKKK activity by systematically testing MAPKKs as candidate substrates, in vitro. We demonstrate that LRRK2 phosphorylates the mitogen-activated protein kinase kinases (MAPKK) MKK3, -4, -6 and -7. MKKs act upstream of the MAPK p38 and JNK and mediate oxidative cell stress, neurotoxicity and apoptosis. The disease-associated LRRK2 G2019S and I2020T mutations show an increased phosphotransferase activity towards MKKs, correlating with the activity shown for LRRK2 autophosphorylation. Our findings present evidence of a new class of molecular targets for mutant LRRK2 that link to neurotoxicity, cellular stress and cytoskeletal dynamics.

Genome-wide association study in Parkinson's disease reveals strong association signals in the SNCA AND MAPT genes

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Background: Parkinson's disease (PD) is the second most common neurodegenerative disorder. The etiology of PD is largely unknown. Epidemiological findings along with genetic association studies highlight a significant genetic contribution to disease risk. However, the genetics of PD have only been partially explained by genes which were identified in large multigenerational families. Genome wide association scans offer a powerful approach to identify common genetic factors that influence the common form of PD.

Objective: To identify variants influencing the susceptibility to sporadic PD.

Methods: We performed a genome-wide association study in PD in 757 cases and 976 neurologically healthy controls. Each individual was genotyped on Illumina genotyping chips (Illumina humanhap550) yielding 561 466 genotypes/individual. SNPs with minor allele frequencies (MAF) > 5%, Hardy-Weinberg Equilibrium p > 0.01 and genotype call rates > 95% were included in the analysis (498 560 SNPs).Top hits were further genotyped in an independent cohort consisting of 1100 cases and 2200 controls. We performed association tests using an additive model.

Results and conlusions: We identified an association, which exceeds the Bonferroni correction, in the SNCA and MAPT genes. Our results suggest that variations in the SNCA and MAPT genes play an important role in the pathogenesis of PD.

Gene expression analysis in dopaminergic neurons of the substantia nigra reveals candidate genes and differentially regulated pathways in Parkinson disease

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Recent discoveries of familial forms of Parkinson disease (PD) have led to the identification of several dysregulated cellular pathways, which are believed to be also involved in the pathogenesis of idiopathic cases. However, the individual contribution of these pathways in idiopathic PD remains elusive, as well as the identification of causative and consequential events that are eventually leading to the predominant and early degeneration of dopaminergic neurons (dN) in the substantia nigra pars compacta (SNc). Microarray gene expression studies are a promising approach for the unbiased identification of genes and key regulatory pathways involved in neurodegenerative disease. We analyzed whole genome expression of dopaminergic cells of human SNc using laser microdissection, in-vitro transcription and microarray analysis. Using a stringent statistical approach (Bonferroni), we have identified four differentially mRNA transcripts, suggesting these genes as potential PD genes. Indeed, SNP analysis confirmed one locus as significantly associated with PD. Additionally, after Benjamin-Hochberg correction, 310 genes were detected as differentially regulated and these were assigned to gene ontology terms. Further statistical analysis showed an enrichment of mitochondrial genes and members of the ubiquitin-proteasome pathway, intracellular signaling pathways, and members of the transcription/translation, as well as the programmed cell death machinery. The transcriptional changes emulate candidate pathways, which have been identified in studies of disease causing genes. This study provides a link to recent findings in cell culture and animal models of PD and verifies cell type specific expression profiling as a valuable tool to identify new disease genes.

Genome wide association study and analysis of candidate genes on nicotine dependence

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The aim of the study is to identify DNA variants being associated with nicotine-related behaviour. Chronic tobacco use due to nicotine dependence (ND) is the leading preventable cause of death and morbidity. Although environmental factors, such as peer smoking and tobacco industry advertising are clearly important in smoking initiation, there is abundant evidence for a genetic component. There are both overlapping and unique genetic influences on smoking initiation, ND, and smoking persistence. It was estimated that additive genetic effects account for 56% of the variance in liability to initiate smoking.

For the identification of genetic vulnerability factors for ND, a genome wide association study (GWA) followed by a validation and replication approach on more than 7000 subjects of European origin from four independent study populations was carried out. Gene regions associated with nicotine-related behavior were identified in the GWA using the Affymetrix 500K Array Set. In parallel a literature-based candidate gene typing was performed. The resulting SNPs were ranked according to the significance of association with the smoker status (>1 cigarette per day), the heavy smoker status (>20 cigarettes per day) and the results of the Fagerström Test for Nicotine Dependence.

In the GWA signals were observed in gene regions previously not known to be implied in addictive behaviour. Currently, the most promising SNPs are being replicated and assessed for specificity in functional studies and also analyzed in respect to intermediate phenotypes. In the candidate gene part of the study several candidate genes including the nicotinic acetylcholine receptor subunits alpha 3 and alpha 5, as well as alpha 4 were significantly associated with nicotine addiction. The nicotinic acetylcholine receptor subunit alpha 4 additionally seems also to be associated with the intensification of nicotine dependence.

QTL analysis of endophenotypes related to alcoholism

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The aim of the present study was the identification of gene loci or quantitative traits that contribute to the development and manifestation of alcohol addiction and related behaviors. For a QTL study design the second filial (F2) generation of a C57BL/6J and C3H/HeJ mice intercross was first phenotyped in paradigms related to alcohol addiction. We examined behaviors including ethanol preference, stress-induced changes in ethanol preference, ethanol-induced hypothermia, tolerance, somatic withdrawal symptoms, withdrawal-induced anxiety and locomotor effects in 600 genetically heterogeneous mice from our intercross. The genotype of these mice was subsequently assessed by microsatellite marker mapping accounting fragment lengths polymorphisms between the alleles of the offspring. QTL contributing to alcohol dependence and related traits were subsequently identified using univariate and bivariate analyses. These analyses were performed with the R/qtl tool, which is an extensible, interactive environment for mapping QTL in experimental crosses. To determine individually-acting QTL, a genome scan using the multiple imputation algorithm was conducted, with a two-QTL genome scan for the full model (two QTL plus interaction) and for the additive model (two QTL but no interaction) interacting loci were analyzed. We detected chromosomal regions for future exploration where no obvious candidate gene has yet been mapped. Additionally, we found QTL that have already been published, thus confirming the impact of these loci on the development and manifestation of alcoholism.

Longitudinal gene-gene and gene-time effects on body mass index for variants near INSIG2 and in the MC4R gene

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With the availability of large cohorts, there is demand for statistical methods for analysis of longitudinal data (i.e., data of individuals with repeated follow-up) which retain their validity and efficiency in a wide range of practical applications. As a step forward in this direction, within NGFN-GEM, we developed a nonparametric longitudinal method to analyze average main effects of genes, gene-gene interaction and gene-time effects for quantitative phenotypes in cohorts. The test considers genetic variants at candidate loci and covariates as factors. It formally resembles a repeated measures ANOVA which is applied to the phenotype mid-ranks. Estimates of the longitudinal correlation account for the dependence structure in the data.

Recently, novel genes have been reported to contribute to regulation of weight. Two of them are INSIG2 and MC4R. However, gene-gene-interaction for follow-up data as well as the influence of these genes on the development of weight over time has not yet been analyzed. We apply our new method to perform nonparametric longitudinal association analysis for longitudinal impact and interplay of the two markers rs7566605 for INSIG2 and rs2229616 for MC4R on body mass index (BMI). We report results for data on 1619 women and 1542 men from the surveys S3 and F3 from the KORA study (Kooperative Gesundheitsforschung in der Region Augsburg), a representative sample of the adult general population of South German nationality. This sample shows evidence for gene-gene interaction between rs7566605 and rs2229616 and for a time-dependent impact of rs7566605 on BMI.

Conversion of the salt-resistant phenotype of spontaneously hypertensive rats into a salt-sensitive phenotype leads to severe cardiac hypertrophy in a new double-consomic rat model

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In linkage analyses between salt-sensitive Dahl (SS) and spontaneously hypertensive (SHR) rats we mapped several QTL linked to salt-sensitive systolic blood pressure (SBP) and hypertensive target organ damage, i.e. left ventricular (LV) hypertrophy (LVH), on rat chromosome (RNO)6 and RNO19, respectively. We tested whether salt-sensitive cardiac damage can be expressed in the SHR background by single and double transfer of RNO6 and RNO19 from SS.

We generated single-consomics and a double-consomic SHR-6SS19SS by transferring RNO6 and/or RNO19 from SS into SHR. We analysed the effect of high-salt for 8 weeks on SBP and cardiovascular organ damage. In contrast to SHR-6SS, SHR-19SS demonstrated a significant increase in SBP vs. SHR (186.5±9.8 vs. 171.5±8.3 mmHg, p=0.03), while both revealed no significant differences in cardiac damage. In SHR-6SS19SS a significant increase of SBP (192.8±13.5 mmHg) vs. SHR was observed (p=0.0002). SHR-6SS19SS demonstrated also a marked increase of the LV weight index vs. SHR (3.3±0.3 vs. 2.6±0.2 mg/g, p< 0.0001) and macroscopic evaluation showed severe concentric hypertrophy. LV interstitial and perivascular fibrosis revealed a significant increase in SS rats (4.9±2.1/15.7±3.2%) vs. SHR (1.7±0.5/7.4±2.4%; p< 0.001, respectively), while SHR-6SS19SS showed no significant differences vs. SHR despite the severe hypertrophy. Cardiomyocyte diameters exhibited no significant differences between SS and SHR, whereas SHR-6SS19SS showed a significant increase vs. SHR (13.8±1.6 vs. 11.6±1.0 µm, p=0.009). Transfer of RNO6 and RNO19 from SS into SHR converts the salt-resistant into a salt-sensitive phenotype. The latter is associated with severe LVH in response to salt-loading. Interestingly, in contrast to SS rats SHR-6SS19SS are protected from cardiac fibrosis development. Thus, this new double-consomic strain can be used to analyze and dissect the molecular mechanisms that are associated with LVH and cardiac fibrosis in salt-sensitive hypertension.

Chromosome 9q21 as a new major susceptibility locus for dilated cardiomyopathy

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Human dilated cardiomyopathy (DCM) causes considerable morbidity and mortality and is one of the major causes of sudden cardiac death. We performed a genome-wide association study with 406 DCM patients (Heidelberg, Germany) and 476 controls from the population based POPGEN Biobank (Kiel, Germany) to identify novel susceptibility loci for dilated cardiomyopathy. Using the standard features for quality control, population stratification detection and association testing as implemented in PLINK, we observed 39 significantly ($P< 5x10-6$) associated SNPs with DCM after correcting for multiple testing using false discovery rate.

38 significantly associated SNPs were selected for validation in 1229 DCM patients (Heidelberg, München and Kiel, Germany) and 1040 controls from the KORA Biobank (Augsburg, Germany). SNP genotyping was performed using TaqMan technology. We excluded two SNPs failing the Hardy-Weinberg equilibrium test ($P>0.001$) and one SNP having a minor allele frequency below 3%. The 35 remaining SNPs were adjusted for sex and age using logistic regression and six significant ($P< 0.05$) loci on chromosome 1, 5, 9, 16 and 21 were detected. The loci on chromosome 9q21 showing a P value of 3.1x10-21 turns out as a new major susceptibility locus for DCM. These regions are currently subject to fine-mapping and further detailed statistical analysis involving clinically relevant phenotypes.

Evolutionary dynamics of gene cluster rearrangements associated with complex diseases

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Unraveling the "organization" of the genome is an important goal in studying genetic variants associated with common diseases, where variants act on intermediate molecular phenotypes that in turn induce changes in complex disease traits. Gene order in the human genome is not random (Hurst 2004). Genes with similar expression patterns involved in the same processes (pathways) tend to form functional clusters. Several studies in Eukaryotes showed that clustering is not only associated with co-expression. It seems that natural selection favours linkage of genes with positive epistatic effects (Nei 1967, Gessler and Xu 1999, Pal and Hurst 2003).

Here, we report that a 600 kilobase (kb) region of linkage disequilibrium (LD) on 5q31.2-3 contains a gene cluster, which is associated with cardiomyopathy in three independent Caucasian populations (combinded P-value = 0.00087). Three independent knockdowns of co-expressed orthologous genes within this cluster in zebrafish resulted in a phenotype of myocardial dysfunction. Evolutionary analysis of the gene cluster suggests that this LD block, associated with heart failure, emerged by several genomic rearrangements. Interestingly, the cluster formation coincides with the evolution of heart anatomy across vertebrates, from two-chamber fish heart to three-chamber amphibian heart to four-chamber avian heart. Our observation supports the hypothesis that selection favours coordinated control of functionally related genes, which jointly determine a complex trait (Lynch and Conery 2003). Furthermore, a genome-wide analysis revealed the presence of numerous clusters containing co-expressed genes, which have undergone several rearrangement events in their evolutionary history. Notably, many of those rearranged gene clusters are associated with a disease phenotype in mice (MGI 4.12 database) and conserved in a causal co-expression network.

Novel Z-disk proteins and cardiac-mechanosensation

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Introduction: Mutations in genes involved in cardiac mechanosensation (mec), such as the muscle LIM protein (MLP) gene, have been shown to cause cardiomyopathy.

Hypothesis: Identification of novel mec genes by searching for new MLP interacting proteins (MiP) and consecutive functional analysis may provide novel insights into molecular mechanisms.

Methods & Results: A yeast 2 hybrid heart cDNA library has been screened and novel MiPs (MiP1, MiP2) have been identified. MiP1 consists of an N-terminal POZ domain and additional 13 carboxyterminal zinc fingers, whereas MiP2 belongs to the MYM domain family of proteins. Both proteins were localized to the cytoskeleton (Z-discs, intercalated-discs) and MiP1 in addition to the nucleus. MiP1 is downregulated in human ischemic and dilated cardiomyopathy (DCM) samples (n=12, p=0.01), whereas MiP2 is transcriptionally induced in DCM (n=12, p=0.001). Screening of 95 DCM patients identified one familial MiP1 missense mutation, not present in 1600 control chromosomes. No additional mutations in 12 known cardiomyopathy disease genes were identified, indicating a disease causing mutation. Luciferase as well as ChIP assays identified calcineurin as a novel Mip1 target gene.
MiP1 and MiP2 conventional knockout animals are embryonically lethal leading to the development of a conditional MiP1 knockout mouse model (CKO). CKO mice failed to adapt to biomechanical stress in form of transaortic constriction (TAC): four weeks after surgery, %FS was significantly decreased (46.5±6.3% versus 52.0±3.7%, P< 0.04) and LVEDD (3.74±0.19% versus 3.44±0.16%, P< 0.003) as well as LVESD (2.00±0.28% versus 1.65±0.14%, P< 0.005) was significantly increased in CKO mice (n=10) compared to WT littermates (n=8).

Conclusions: MiP1 and 2 are novel MLP interacting proteins with potentially important implications in cardiac mechanosensation. In addition, MiP1 mutations might be a novel cause of human cardiomyopathy.

A genome wide association study reveals SLC2A9 as a major gene for uric acid levels with pronounced sex-specific effects

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Introduction: Serum uric acid (UA) levels are correlated with gout and clinical entities such as cardiovascular disease and diabetes. Heritability of UA levels has been shown repeatedly. We aimed to search for genes involved in the regulation of UA levels in a genome-wide association study.

Methods: A genome-wide association study was carried out on the KORA F3-500K study.

Results: We identified a QTL associated with UA levels located on chromosome 4 including 40 SNPs with P-values below the genome-wide significance level. The most significant SNPs mapped within intron 4 and 6 of SLC2A9 (effects -0.18 to -0.36 mg/dL per copy of the minor allele). These findings were replicated in three independent samples from Germany (KORA S4 and SHIP) and Austria (SAPHIR) with P-values ranging from $1.2x10^{-8}$ to $1.0x10^{-32}$. In addition the SLC2A9 genotypes showed significant association with self-reported gout and showed pronounced sex differences. The proportion of the variance of serum UA levels explained by genotypes was about 1.2% in men and 6% in women. Analysis of whole blood RNA expression profiles from a KORA F3-500K subgroup (n=117) revealed a significant association between the SLC2A9 isoform 2 and UA levels. SLC2A9 encodes a transporter protein (GLUT9) that belongs to class II of the facilitative glucose transporter family. In an ongoing meta-analysis with more than 20.000 genome-wide scans we confirmed the previous finding and identified several additional loci associated with UA levels.

Discussion: Our expression studies allow discrimination between two annotated isoforms of this gene. The significant association with the shorter protein GLUT9DN argues for a prominent role of the SLC2A9 isoform 2 in the regulation of UA concentrations. The association with the isoform 2 suggests an involvement of the protein in UA excretion.

Reference: Döring A, Gieger C et al. SLC2A9 influences uric acid concentrations with pronounced sex-specific effects. Nat Genet. 2008; 40(4):430-6.

Applicability and relationship of E/e', LAVI, age, natriuretic peptides and hypertrophic markers in diastolic dysfunction and diastolic heart failure

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Diagnosis of early stages of diastolic heart failure remains elusive. We determined the prevalence of diastolic dysfunction in patients at risk and evaluated the role of established and novel parameters in the diagnosis of asymptomatic diastolic dysfunction (diaDF) or symptomatic diastolic heart failure (diaHF).

Methods: We established a prospective cohort of 1344 ambulatory general practice patients (583 male, 761 female) with at least one risk factor for diastolic dysfunction (hypertension, diabetes, sleep apnoea). Diastolic function was assessed by comprehensive echocardiography (including $E/e'_{lat.}$), left atrial volume index (LAVI) and the hypertrophy markers left ventricular mass index (LVMI) and intraventricular septum thickness (IVS). NT-proBNP, NT-proANP levels were measured in parallel.

Results: Overall prevalence of diaDF was 85.7%. Older patients more often suffered from symptoms of heart failure (70.0% of patients □80 years). In patients with DDF, there was a significant increase in LAVI and natriuretic peptides with inreasing severity of DDF (grade 1 vs. grade 2/3 DDF: LAVI: 22.6±0.3 vs. 27.2±0.8ml/m²; NT-proBNP: 129.1±7.0 vs. 215.7±27.0pg/mL; NT-proANP: 4060.4±85.5 vs. 6219.9±1827.8pg/mL; all $p< 0.01$). However, LAVI and natriuretic peptides did not significantly differ between DDF and DHF patients. In contrast, $E/e'_{lat.}$ values were higher in patients with diaHF compared to patients with asymptomatic diaDF with $p < 0.05$ in the higher age groups (71-80 years: 10.8±0.3 vs 9.5±0.2; □80 years: 12.6±0.9 vs 11.3±0.8). Furthermore $E/e'_{lat.}$ correlated well with the hypertrophy markers LVMI ($r = 0,46$) and IVS ($r = 0,31$).

Conclusion: The prevalence of DDF and DHF increased with age and was accompanied by an increase in LAVI and natriuretic peptides. In advantage to these diagnostic factors the tissue Doppler parameter $E/e'_{lat.}$ was able to differentiate between diaDF and diaHF and correlated well with the degree of cardiac hypertrophy.

Genome-wide association analysis of left ventricular hypertrophy and diastolic heart failure

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Diastolic heart failure is an increasingly recognized condition with hypertension and cardiac hypertrophy as some of the major risk factors. Yet, the exact molecular mechanisms and genetic predisposition remain to be elucidated. We performed a whole genome association study for single nucleotide polymorphisms (SNPs) and markers of diastolic function and cardiac hypertrophy.

Methods: DNA was isolated from 584 whole blood samples taken from patients participating in an epidemiological study of the German Competence network heart failure (KNHI). All patients received detailed echocardiography. Diastolic dysfunction was quantified by tissue doppler (parameter E/E') and cardiac hypertrophy by the left ventricular mass index (LVMI). A case control study design was chosen and analysis performed by Cochrane-Mantel-Haenszel test. Accounting for sex and age was possible with this test.

Results: For the association with E/E' a number of 112 SNPs showed a p-value < 0.0003 corresponding to a starting point for deviation from the expected p value distribution in the QQ-plot. Only 2 SNPs deviated from the Hardy Weinberg equilibrium. We observed 15 LD-Blocks where for each of them at least 2 of the top 112 SNPs belong to. In a second analysis the association with LVMI in hypertensive patients was tested and revealed 39 SNPs with a p-value < 0.0001. Among the found targets were genes with potential role in cardiac ion homeostasis such as a transient receptor potential cation channel and a calcium channel subunit.

Conclusion: The results are promising to find genetic associations with conclusive biological context in diastolic function but require confirmation in a larger population.

Novel susceptibility locus for coronary artery disease on chromosome 3q22.3

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By the year 2020, CAD and its major clinical manifestation MI are expected to be the leading causes of death world-wide. Thus far, GWAS of CAD focused on a few chromosomal regions with strong statistical signals. We hypothesize that applying too stringent statistical thresholds on the association tests´ P-values may prevent one from detecting SNPs with modest effects or/and low allele frequency.

We present a three-stage analysis of 1) genome-wide SNP data in 1,222 German cases with myocardial infarction and 1,298 controls, 2) in-silico replication of loci showing P-values < 0.001 in three additional genome-wide data sets including 5,768 coronary artery disease (CAD) cases and 7,657 controls, and 3) subsequent large-scale replication in 12,417 CAD cases and 12,411 controls of SNPs significant in at least two of the in-silico replication studies. In addition to known loci (9p21.3 and 1q41) we identified one novel locus on 3q22.3 to be significantly associated with CAD. SNP rs9818870 in the MRAS gene shows a combined P-value of P=7.44x10-13 [OR 1.15 95% CI, 1.11 to 1.19] in a total of 19,407 cases and 21,366 controls. In addition, we identified suggestive evidence for association with CAD in the TCF1/C12orf43 gene region (SNP rs2259816: combined P-value of 4.81x10-7 [OR 1.08 95% CI, 1.05 to 1.11]).

In conclusion, analysis of a novel GWAS followed by in-silico replication in three GWAS and a large-scale replication study identified one novel gene locus for CAD (SNP rs9818870) with solid statistical evidence and a second locus (SNP rs2259816) with strong evidence as a new susceptibility locus for CAD.
Further functional work (re-sequencing, fine-mapping) is needed to define the mechanisms by which these novel loci translate into a higher risk of CAD, and whether this information can be used to improve prevention, prediction or treatment of this common condition.

Systematic pathway-analysis of Kinesin Protein Family (KIF) using genome-wide SNP data in patients with myocardial infarction: Genetic variation in KIF17 gene associates with myocardial infarction

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Objectives: Kinesin proteins constitute a large protein family involved in ATP-binding and intracellular transport. A KIF 6 variant (rs20455), has been described to be associated with 24% increased risk of coronary artery disease (CAD) and 34% higher risk of myocardial infarction (MI) . Aim of our study was to perform a pathway analysis of genes encoding KIF.

Methods: Identification of relevant genes was undertaken via medical literature [pubmed] and internet databases [Entrez Genes, HapMap]. Available SNPs were investigated in silico in two independent genome wide SNP data sets (GerMIFSI [875 MI Cases, 1644 Controls] and GerMIFSII [1222 MI Cases, 1298 Controls]). GerMIFSI was genotyped with 500K Affymetrix SNP Array and imputed using the MACH 1.0 algorithm, GerMIFSII was genotyped with Affymetrix 6.0 Array. GWA-data pathway coverage was assessed by generating linkage disequilibrium unit (LDU) maps of HapMap data. Haplotype analysis was carried out.

Results: In KIF pathway, 25 genes were identified. The gene encoding for KIF17 (chr1p36.12), carried three SNPs significantly associated with MI in GerMIFS I and GerMIFS II: rs479323, rs561471 and rs683936. Haplotype analysis confirmed results.

GerMIFS I / GerMIFS II RS_ID / CHR / BP / P-value / OR / P-value / OR

rs479323 / 1 / 20885162 / 0,001045 / 1,748 / 0,001684 / 1,579

Rs561471 / 1/ 20884401 / 0,001688 / 1,756 / 0,0001594 / 1,815

rs683936 / 1 / 20895240 / 0,0005217 /1,686 / 0,03444 / 1,296

Conclusions: Three KIF17 SNPs revealed highly significant results for MI in GerMIFSI and GerMIFSII. Our preliminary results support a significant relation between SNPs of KIF 17 and MI risk.

First genome-wide association study in patients underwent Coronary Artery Bypass Grafting (CABG) under gender specific perspectives

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Background: Twenty-three reports on gender specific mortality after CABG under extracorporeal circulation (ECC) in the medical literature, recruited by several cardiac surgery departments worldwide, describe an average mortality rate of 3.3% in men and 7.1% in women. Reported clinical gender related diagnostic and therapeutic differences are not capable of interpreting this mortality difference between men and women. Female gender seems to be a significant risk factor in many multivariate analyses. Our hypothesis is, that genetic factors play a major role in this gender-specific outcome after coronary artery bypass grafting under ECC.

Patients and methods: We performed a genome-wide association study in patients from the German Myocardial Infarction Family Study (GerMIFS I and GerMIFS II, CABG: 384 men and 115 women, CAD patients: 368 men and 195 women) using genotype information based on imputed SNP data from an Affymetrix 500K and 1M Array. GWA studies received quality control for minor allele frequency □ 1%, p-value of deviation from Hardy-Weinberg Disequilibrium □ 0.001, Armitage's p-trend test was □ 10^{-7}.

Results: In an exploratory analysis of GWAS data we identified 20 SNPs clustering in 16 genomic regions identified which were significant between both groups (p-value between $2.36x10^{-06}$ and $2.66x10^{-11}$). Gender adjusted analysis revealed 8 SNPs in 5 regions (p-value range $5.86x10^{-06}$ and $9,31\ x10^{-06}$) with a stronger effect in women. Replication with other data sets is currently underway and the results of this analysis will be reported.

Conclusions: This is the first genome-wide association study in CABG patients. Several SNPs were significant among groups and interaction of gender could be demonstrated.

No association between monocyte chemoattractant protein-1 (MCP-1) gene polymorphisms and incident type 2 diabetes mellitus (T2DM) in middle-aged men and women: results from the MONICA/KORA Augsburg case-cohort study, 1984-2002

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Background: It has been suggested that circulating levels of MCP-1 could be modulated by genetic variations within the gene coding for this protein, thereby accounting for the possible association between MCP-1 concentrations and risk of incident coronary heart disease (CHD) as well as incident T2DM. Here we prospectively investigate whether various SNPs, covering the whole region of the CCL2 gene, might be associated with incident T2DM.

Methods: A case-cohort study was conducted in initially healthy, middle-aged men and women based on data from the MONICA/KORA Augsburg studies collected between 1984 and 2002 (mean follow-up 10.1 yrs). Concentrations of MCP-1 were measured in 498 case subjects (307 men, 191 women) with incident T2DM and 1569 non-case subjects (835 men, 734 women). Taking into account possible gender differences, all analyses were carried out for men and women separately. Genotyping of 6 SNPs (rs1024610 (-2136A/T) and rs2857656 (-362C/G) in the promoter region; rs2857657 (+763C/G) in intron 1; rs4586 (+900C/T) in exon 2; rs13900 (+1542C/T) in exon 3, and one SNP in 3' flanking region (+3726T/C, rs2530797) was performed on the Sequenom MALDI-TOF MS system.

Results: MCP-1 genotype distribution did not significantly differ among subjects with type 2 diabetes and non-case subjects (n = 2,067). We found no consistent association between these 6 SNPs within the CCL2 gene and incident T2DM in crude and in multivariable adjusted analyses, neither for men and women separately, nor in a model that included all study participants.

Conclusions: Despite the fact that polymorphic alleles of rs1024610 and rs2857657 strongly contributed to increased MCP-1 concentrations in women in our previous study, no association was found between these 6 SNPs within the CCL2 gene and incident T2DM during mean 10-year follow-up.

Monocyte chemoattractant protein-1 (MCP-1) gene polymorphisms, MCP-1 plasma levels and incident coronary heart disease (CHD) in middle-aged men and women: Results from the MONICA/KORA Augsburg case-cohort study, 1984-2002

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Background: MCP-1, a novel chemokine plays a pivotal role in the recruitment of monocytes into atherosclerotic plaque. It has been suggested that genetic variations within the MCP-1 gene (CCL2) might modify circulating MCP-1 levels. We prospectively investigated whether various SNPs within the CCL2 gene, affect MCP-1 concentrations and whether these SNPs account for an increased risk of future CHD events.

Methods: A case-cohort study was conducted in initially healthy, middle-aged subjects, based on data from the MONICA/KORA Augsburg studies collected between 1984 and 2002 (mean follow-up 10.9 yrs). MCP-1 levels were measured in 324 case subjects (252 men, 72 women) with incident CHD (fatal/non-fatal MI and coronary death) and 1736 non-case subjects (903 men, 833 women). Genotyping of 6 SNPs (rs1024610; rs2857656; rs2857657; rs4586; rs13900; rs2530797) was performed on the Sequenom MALDI-TOF MS system.

Results: No consistent association was found between various SNPs within the CCL2 gene and incident CHD in crude and in multivariate adjusted analyses in the whole population. Only rs2530797 GG-genotype in women was associated with 2-fold increased risk for CHD. MCP-1 baseline concentrations in female participants from the randomly drawn subcohort (n=1,834, 983 men, 851 women) were also significantly modulated by two of the 6 analysed DNA variants (rs1024610 and rs2857657). In particular, for rs1024610, age- and survey adjusted MCP-1 plasma levels were 160.3 vs 187.5 vs 199.4 pg/mL for TT (n=549) vs TA (n=269) vs AA (n=33) genotype carriers, respectively (p trend=0.003); whereas no accociations between these 6 SNPs and MCP-1 baseline concentrations were found in male participants.

Conclusions: Despite the fact that polymorphic alleles of rs1024610 and rs2857657 strongly contributed to increased MCP-1 concentrations in women, no consistent association was found between these 6 SNPs within the CCL2 gene and incident CHD.

No association between C-reactive Protein (CRP) gene polymorphisms, CRP haplotypes and incident type 2 diabetes mellitus (T2DM) in middle-aged men and women: results from the MONICA/KORA Augsburg case-cohort study, 1984-2002

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Background: It has been suggested that circulating levels of CRP could be modulated by genetic variations within the gene coding for this protein, thereby accounting for the independent association between CRP concentration and risk of incident T2DM. Here we prospectively investigate whether various SNPs within the CRP gene might be associated with incident T2DM.

Methods: A case-cohort study was conducted in initially healthy, middle-aged men and women based on data from the MONICA/KORA Augsburg studies collected between 1984 and 2002 (mean follow-up 11.0 yrs). Concentrations of CRP were measured in 435 case subjects with incident T2DM and 1,408 non-case subjects. Genotyping was performed on the Sequenom MALDI-TOF MS system.

Results: We analysed four SNPs: two in the promoter (rs3091244; rs2794521), one intronic (rs1417938), one exonic (rs1800947). Haplotype estimation yielded 5 haplotypes with frequencies □5% (GATT 30.5%, GTCC 28.0%, GTCT 27.3%, CTCT 7.3%, GTAT 6.5%). All other haplotypes were pooled in a group of rare haplotypes. Neither the 4 different SNPs, nor the 5 more common haplotypes were found to be consistently associated with incident T2DM in crude and in multivariable adjusted analyses, neither in a model that included all study participants, nor for men and women separately. In particular, with respect to the intronic SNP rs1417938, subjects, bearing the TA genotype (n=805) or subjects homozygous for the A allele (n=163) compared to TT genotype carriers (n=875) showed no significant increase in the risk for incident T2DM (HR 0.91, 95% 0.70-1.18; and HR 1.24, 95% CI 0.80-1.91, respectively).

Conclusions: These data therefore suggest that these SNPs within the CRP gene do not play a major role in the susceptibility to T2DM in initially healthy subjects, despite the fact that individuals, carrying several of these polymorphic alleles (e.g. A allele of rs1417938) were exposed to moderately elevated CRP concentrations long-term.

Comparative mapping of linkage and association results in myocardial infarction

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Our group established a large collection of myocardial infarction (MI)-families with 2-5 affected first-degree relatives and large collection of unrelated MI cases and controls. Genome-wide microsatellite linkage analyses on MI sibling-pairs and two genome-wide association (GWA) studies on unrelated MI cases (n=875 (GerMIFSI)/ n=1220 (GerMIFSII)) and controls (n=3000) were carried out. Our current approach assumes that the same genes involved in rare autosomal dominant forms of MI may also be associated with the risk for MI in the general population.

25 families with an autosomal dominant inheritance pattern were analyzed by cosegregation analyses. Genome-wide scanning was performed using high-density SNP arrays (Affymetrix 500K and 6.0 arrays). Data analysis was performed in a three-step procedure. First, the large chromosomal regions were reduced to so called "interesting regions", based on the fact that these genes additionally display an association with MI in one of the two GWAs. The second step comprises the decrease of these "interesting regions" to "top regions" with positive SNPs replicating in the other GWAS. These "top regions" include only few genes or intergenic regions. Sequencing of these regions is the third step.

With the genome-wide microsatellite linkage analysis in 25 families (including n=569 individuals) five chromosomal regions 1q42.3; 4q31.21: 4q34.1; 8q24.13 and 17q24.2 were identified. In the same chromosomal regions we have found significant association for several SNPs tested in two GWAS. With systematic data analyses we reduced the chromosomal region to top regions encompassing only several genes or intergenic regions. For example, the 8q23.3-q24.4 locus (approx. 80 genes) was reduced to four top regions, including *FOG-2*, *MTSS1* and *ZHX2*.

The comparative analysis of linkage and GWAS data allows the reduction of linkage intervals leading to a much smaller number of genes to be sequenced in order to identify the underlying mutations.

From genomics to transcriptomics - genome-wide association - and expressionanalyses in the population-based Gutenberg Heart Study

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Cardiovascular disease is one of the main causes of death in the world. Since traditional risk factors cannot completely explain the susceptibility for cardiovascular disease, the search for novel risk indicators and the deciphering of underlying mechanisms involved in the pathogenesis of cardiovascular diseases is of prime importance.

The Gutenberg Heart Study (GHS) is a prospective population-based cohort study started in 2006. Beside classical clinical and anthropometric data, numerous intermediate clinical and laboratory phenotypes are colleted for each participant. One of the major focuses of the GHS is to explore the genetic roots of cardiovascular diseases.

In a Genome-Wide Association (GWA) study, DNA of 3.500 study participants was genotyped using the Human Genome-Wide SNP 6.0 Array (Affymetrix). Furthermore, in a Genome-Wide Expression (GWE) study using Illuminas´ HumanHT-12 Expression BeadChip, analysis of the transcriptome of 1.600 study participants (same participants for whom GWA data were available) was conducted.
Data sets were analyzed individually and in parallel in regard to the same intermediate phenotypes in order to explore not only genetic variants/genetic loci associated with certain intermediate phenotypes but also to explore changes in gene expression at these loci and/or the influence of genetic variants on gene expression. The general concept of genetic analyses in the GHS will be described.

A genome-wide association analysis of HDL-cholesterol in the population-based KORA study sheds new light on intergenic regions

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High-density lipoprotein cholesterol (HDLC) is a strong risk factor for atherosclerosis and assumed to be under considerable genetic control. We aimed to identify gene regions influencing HDLC levels by a genome-wide association (GWA) analysis in the population-based KORA Study.

In KORA S3/F3 (n=1,643), we analyzed 377,865 SNPs (500K Affymetrix), complemented by GWA results from the Diabetes Genetics Initiative (DGI, n=2,631) and by replication data from KORA S4 (n=4,037) and the Copenhagen City Heart Study (n=9,205).

Three SNPs showed consistent associations in subsequent replications: one SNP 10kb upstream of CETP (pooled p-value=$8.5*10^{-27}$), one SNP about 40kb downstream of LIPG (p-value=$4.67*10^{-10}$), both independent from previously reported SNPs, and one from an already reported region of LPL (p-value=$2.82*10^{-11}$). Bioinformatic analyses indicate a potential functional relevance of the respective SNPs.

Our GWA study identified two interesting HDLC-relevant regions upstream of CETP and downstream of LIPG. This draws the attention to the importance of long-range effects of intergenic regions which may impact future candidate gene association studies towards extending the analyzed region.

Our study reinforced CETP and LPL as HDLC genes and thereby underscores the power of our study and of this type of GWA approach to pinpoint associations of common polymorphisms with effects explaining as little as 0.5% of the HDLC variance in the general population.

No association between the connexin37 gene polymorphism C1019T and myocardial infarction in a German population

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Background: Connexin genes (Cx) encode for important gap junction proteins. In an ApoE-Cx37 double knockout mouse model Cx37 has shown to protect against atherosclerosis (Wong et al., Nat Med 2006). In human the C1019T polymorphism (rs1764391) has been shown to be associated with myocardial infarction or coronary artery diseases (MI / CAD) in various populations.
The aim of this study was to further replicate the association of the C1019T SNP in a large German MI sample with a strong familial background for MI (GerMIFS).
Materials: The C1019T SNP was genotyped by Taqman technology in 1,156 MI cases from the German Myocardial Infarction Family Study (GerMIFS) and 983 controls from KORA/MONICA S3. For subgroup analyis , 877 of the patients were grouped by systematic evaluation of coronary angiograms into patients with coronary artery calcification (CAC, n=615) and without CAC (n=262). Differences in genotype frequencies were evaluated by an asymptotic two-sided Cochran Armitage trend test.

Results: No significant difference between the minor allele frequency (MAF) of the C1019T T allele in patients with CAD (MAF: 30.9%) and controls (MAF: 29.3%) (p=0.2658). Furthermore, we didn't find an association between the SNP in patients with CAC (MAF: 34.1%) and without CAC (MAF: 32.3%; p=0.5496).

Conclusion: The connexin37 C1019T SNP is neither related with CAD nor CAC in the GerMIFS.

Association of SNP rs671699 in the connexion 37 gene with coronary artery calcification

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Background: The connexin gene 37 (Cx37) is located on human chromosome 1p36.1, a region previously identified to contain a locus associated with myocardial infarction or coronary artery disease (MI/CAD). To further investigate the role of Cx37 in MI/CAD patients we investigated SNPs within Cx37 in the German Myocardial Infarction Family Study (GerMIFS).

Materials: 97 known SNPs within the Cx37 were retrieved from the "snpper" website and tested in-silico in our imputeted Affymetrix® Human Mapping 500K Array Set data set (GerMIFSI) to select new informative SNPs for further Taqman analysis. To verify the association, the identified in-silico SNPs were genotyped in 1,156 MI cases from GerMIFS and 983 controls from KORA/MONICA S3. Differences in genotype frequencies were evaluated by an asymptotic two-sided Cochran Armitage trend test (CATT). Second, 877 of the MI patients were grouped by systematic evaluation of coronary angiograms into patients with severe coronary artery calcification (CAC, n=223), moderate CAC (n=392) and without CAC (n=262). Differences in genotype frequencies between CAC groups were evaluated by an asymptotic two-sided Jonckheere-Terpstra Test (JTT).

Results: Based on the in-silico analysis, two SNPs within the Cx37 were identified to be significantly associated with MI (p=0.0014 for rs540458 and p=0.0006 for rs671699). Both SNPs are located in the same haplotype block. For this reason we only selected the rs671699 SNP for further analysis on Taqman. No significant association between the rs671699 SNPs and MI could be found (p_{CATT}=0.5310). Interestingly, CAC analysis showed that the minor allele frequency (MAF %) of the T allele increases significantly with the severity of CAC (22.30% (MI without CAC), 24, 90% (MI with moderate CAC) and 29.59% (MI with severe CAC; P_{JTT}=0.0170)).

Conclusion: In our large sample of MI patients the new identified rs671699 SNP is not associated with MI however we demonstrated an increase risk for CAC.

Analysis of copy number variation in a population based study using high density SNP microarrays

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Whole genome analysis using high-density single-nucleotide-polymorphism (SNP) oligonucleotide arrays allows identification of copy number variable regions (CNV) across the human genome. We studied DNA of 708 individuals who are part of the population based KORA study using Illumina Hap550 arrays.
Data analysis was carried out by median normalization and genotype-specific dosage calculation using R-scripts. Raw intensity values were hierarchically clustered before CNV analysis to remove outliers showing an extreme intensity profile. For analysis, we divided the arrays in three different clusters. We further excluded those arrays with a $\log_2$ intensity ratio MAD > 0.14, leaving 519 individuals (82%) for the analysis. For CNV calling strict criteria was employed requiring each candidate region to have at least 10 supporting SNPs. Using another dataset, we have previously shown by quantitative PCR that this threshold results in a false positive detection rate of < 5%.

We identified 1805 CNVs (1284 loss events, 521 gain events) corresponding to 670 distinct CNV loci across the human genome. The mean and median CNV length was 119.282 and 60.760, respectively and 3.6% of the human genome are covered by CNVs. 39.5% of these CNVs are novel and previously not described in the Database of Genomic Variants (DGV), whereas 60.5% of the CNV loci display >33% CNV length overlap with known DGV loci (mean overlap length 80.9%). 309 of the observed CNV loci are identified in more than one individual, while 361 CNVs are singletons (98 > 1% MAF, 25 > 5% MAF, 11 > 10% MAF). In total 127 CNVs (7.03%) overlapped with genes known to be associated with human diseases according to the OMIM database.

In summary, we present a high quality dataset resulting in 3.6 CNVs per individual and showed that CNV analysis is highly dependent on the experimental quality and the comparability of the intensity profiles. In our opinion, quality issues in CNV analysis deserves further attention.

Characterisation of a new ENU induced mouse model for Polycytemia Vera

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MVD013 was established within the Munich ENU mouse mutagenesis project. The male founder animal was selected due to changes in the red blood cell count in the clinical chemistry screen. The phenotype was dominantly inherited and fully penetrant in the confirmation cross. Heterozygous mutant mice have an increased red blood cell count, elevated haemoglobin and haematocrit values as well as a reduced mean corpuscular volume. Additionally, gastrointestinal tumours are found at the ileum and caecum of almost all aged mutant mice. Human diseases comparable to these phenotypes are Polycythemia Vera (PV) and gastrointestinal stromal tumour (GIST). PV, a myeloproliferative disorder, affects both sexes of all ethnic backgrounds and occurs preferentially at the age of 50-70 years. GIST is a rare tumour of the gastrointestinal tract (1-3% of all gastrointestinal malignancies) which is thought to arise from interstitial cells of Cajal (ICC), which are a part of the autonomic nervous system of the intestine. They serve as a pacemaker in controlling the intestinal motility. SNP analysis mapped the mutation to the chromosome 5 between 67.85 Mb and 80.03 Mb. In this region there are several candidate genes, including c-kit and PDGFR□ as the most important. C-kit, a protein kinase transmembran receptor, was described as a proto-oncogene and is associated with Polycytemia Vera and anaemia. It is presently analysed for mutations in the coding region and regulatory sequences. Other candidate genes, PDGFR□ will be analysed analogously. In parallel, further systematic investigations on the phenotype of MVD013 will be carried out in the German Mouse Clinic (GMC). In total, phenotypic and genetic analysis will reveal the valuation of MVD013 as a model of the human Polycythemia Vera and gastrointestinal stromal tumour.

Large scale quantitative analysis of tumor samples using protein microarrays

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Protein microarrays emerged as antibody-based tool for high throughput proteomics. We have adapted the reverse phase protein microarray approach (RPPA) to greater accuracy by introducing new steps for sample normalization and quality conrol. This approach was named IPAQ (infrared-based protein detection arrays with quantitative readout [1]. We have employed the IPAQ approach for the comparative analysis of snap-frozen tumor samples derived from different tumor entities. Technically, three tumor samples were dissected from a single tumor and subjected to lysis. Tumor lysates were deposited on nitrocellulose-coated glass slides and replicate slides were incubated with antibodies recognizing cancer-relevant proteins. All antibodies were previously characterized by Western blotting using appropriate samples. Only antibodies recognizing a single band were used on protein microarrays.

With these highly specific antibodies, the detection of a specific protein or a certain phosphorylation-site can be performed. Protein profiling can be done from as little as only 20,000 cells (derived from *in vitro* experimentation) and with a sensitivity in the fg protein/nl lysate range [1]. The current capacity is limited to the analysis of up to 1000 different samples per microarray. Routine IPAQ applications involve analyzing the activation status of signaling pathways, for example after RNAi-based silencing experiments or growth factor stimulation and of tumor samples. Results from tumor profiling and mutational analysis will be presented.

1. C. Loebke et al. Infrared-based protein detection arrays for quantitative proteomics. Proteomics 2007, 7, 558-564.

Identification and characterization of new clinically applicable target proteins in prostate cancer

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The prostate-specific antigen test (PSA) has been a major contributing factor for diagnosis of prostate cancer (PCa). The low specificity limits its use in early detection of prostate cancer. Disease specific protein signature need to be established to identify new targets for diagnosis and treatment options. In this study using 2-DE followed by MALDI-TOF-MS-MS we analysed biopsy samples from benign hyperplasia (BPH) and PCa patients. Results revealed 88 spots representing 79 proteins are significantly ($p < 0.05$) differentially expressed among BPH and PCa groups. The proteins list includes prostatic acid phosphatase precursor (PPAP), enzymes, chaperons, tumor suppressor and cytoskeletal proteins.

Among them the role of tumor protein D52 (TPD52) in PCa progression was investigated in detail. Proteomic data showed of TPD52 overexpression on the protein level while its transcriptional upregulation was demonstrated by real-time PCR. Further, we analyzed the response of the LNCaP prostate cells to altered TPD52 expression. TPD52 overexpressing cells showed an increased proliferation rate whereas depleted cells showed a reverse effect. Depletion of TPD52 in LNCaP cells resulted in cell death which is further confirmed as apoptosis. Additionally, we found that TPD52 promotes cell migration via □v□3 integrin in LNCaP cells through activation of the protein kinase B (PKB/Akt) pathway. TPD52 is localized into mitochondria of LNCaP cells. To identify interacting proteins for TPD52, GST pulldown assays followed by co-immunoprecipitation confirmed its interaction with peroxiredoxin1 *in-vitro*.

In conclusion, it appears that TPD52 is involved in different molecular processes, such as regulation of apoptosis, proliferation and cell migration suggests a role in tumor dissemination. From the proteomic data systems biology network analysis will be performed using metacore software (GeneGo) to elucidate the pathways and interaction networks in which altered proteins are involved.

Antibody-based signal amplification improves specific target detection on reverse phase protein arrays

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Reverse phase protein arrays (RPPA) are suitable for analyzing biological sample sets in a high throughput format. Tyramide signal amplification (TSA) has widely been used for signal detection on protein microarrays. However, lysate analysis with TSA has recently been shown to create unspecific signals when compared to direct detection. Here, we present a novel antibody-based signal amplification strategy. We used JNK and p38 as spike-in proteins to compare the performance with standard detection and TSA. Comparison with direct detection and TSA revealed several advantages of our approach: First, amplification provides higher signal/noise ratios in serial dilutions of complex biological samples. Second, the analysis of specific tumor markers in different tissue lysates showed that our assay reduces unspecific binding when compared to TSA. We established an automated procedure of this method and adapted it to our sensitive detection system IPAQ (infrared-based protein arrays with quantitative readout; Loebke, C. et al., Proteomics 2007, 7, 558-564.). We conclude that the novel method of antibody-based signal amplification is a convenient and cost-effective approach for robust and specific quantification of proteins with RPPA.

Low level HER2 overexpression is associated with rapid tumor cell proliferation and poor prognosis in prostate cancer

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The HER 2 oncogene (also known as c-erbB-2) is involved in the biology of many different tumor types and serves as a prognostic marker and a therapeutic target in breast cancer. In contrast with its known importance in breast cancer, the significance of HER 2 expression and gene amplification in prostate cancer remains highly controversial. In order to learn more on the prevalence and clinical significance of HER2 amplification and overexpression in prostate cancer, a tissue microarray (TMA) containing 2514 primary prostate cancers treated by radical prostatectomy was used. TMA sections were analyzed on protein and DNA level using two different antibodies (HercepTest, Novocastra NCL-CB11) and Fluorescence in situ Hybridization (FISH). The immunohistochemical analyses showed highly similar results for both antibodies. Detectable HER2 immunostaining was observed in 17.2 % for the HercepTest and in 22.5% for the Novocastra antibody with the vast majority of cases showing 1+ or 2+ staining. For both antibodies significant associations were found between positive staining and high grade ($p<0.0001$), advanced pT stage ($p=0.0015-<0.0001$), rapid tumor cell proliferation ($p<0.0001$) and poor prognosis ($p<0.0001$). HER2 amplification was only found in 1 of 2514 cases (0.04%). It is concluded that low level HER2 overexpression occurs at relevant frequency in prostate cancer and in the absence of gene amplification. HER2 protein overexpression may potentially lead to an aggressive behaviour of tumor cells potentially through stimulation of tumor cell proliferation since HER2 expression was shown to be significantly associated with Ki67 Labeling Index.

Chromosome 8p deletions and 8q gains are associated with tumor progression and poor prognosis in prostate cancer

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Deletions of 8p and gains of 8q belong to the most frequent cytogenetic alterations in prostate cancer. The target genes of these alterations and their biological significance are unknown. To determine the relationship between these changes and prostate cancer phenotype and prognosis more than 2000 prostate cancers were analyzed in a tissue microarray format. Both 8p deletions and 8q gains increased in number during different stages of prostate cancer progression. 8p deletions/8q gains were found in 26.08% / 4.88% of 1292 pT2 cancers, 38.18% / 9.87% of 385 pT3a cancers, 42.63% / 11.16% of 251 pT3b cancers, 39.1% / 34.8% of 23 nodal metastases, 30.4% / 19.6% of 46 bone metastases, and 45.45% / 59.1% of 22 hormone refractory cancers ($p < 0.0001$ each). Both 8p deletions and 8q gains were also significantly associated with high Gleason grade ($p < 0.0001$ each) and with each other. In primary tumors, 8p deletions were seen in only 29.3% of 1882 cancers without 8q gain but in 58.9% of 129 cancers with 8q gain ($p < 0.0001$). Among cancers treated with radical prostatectomy, both 8p deletions ($p=0.0019$) and 8q gains ($p=0.0189$) were associated with early PSA recurrence. This prognostic role of 8p deletions did not hold, however, in multivariate analysis. It is concluded, that both 8p deletions and 8q gains are associated with prostate cancer progression. The sharp increase of 8q gains from primary prostate cancer to metastases and recurrences argues for a particular role of one or several 8q genes for progression towards life-threatening disease.

Genome-wide association study for colorectal cancer in German familial cases and replication in independent cohorts

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Genetic susceptibility of colorectal cancer (CRC) accounts for ~30% of its aetiology. Rare, high-penetrance germline mutations in a few genes (mainly APC and DNA mismatch repair genes) account for less than 5% of CRC cases. Much of the remaining variation in genetic risk is supposed to be attributable to common susceptibility loci, each exerting a small influence on risk. We used our genome-wide scan data obtained from 371 German familial CRC cases and 1263 healthy controls using the Affymetrix Genome Wide Human SNP 6.0 Array. The array contains 906.000 SNPs and 946.000 probes for copy number variation (CNV) analysis. Polymorphisms with MAF < 0.05, call rate < 95%, or Hardy-Weinberg equilibrium exact p-value < 10^{-5} in the control group, as well as samples with call rate < 90%, were excluded. From the 875 SNPs with p_{allele} < 10^{-4}, we selected markers with reliable clustering plots for replication, using additionally the following criteria: several SNPs within/close to a gene, location in candidate genes or in already known risk loci for CRC, and coding polymorphisms. Genotyping of the first selected SNPs is currently ongoing in two independent replication cohorts, one of German (655 familial CRC cases and 760 controls) and one of Czech origin (752 CRC cases and 755 controls) using KASPar assays. Further SNPs will be genotyped with the multiplex MALDI-TOF mass spectrometry (Sequenom) system. CNVs were detected by using Genotyping Console 3.0 software implementing the Canary algorithm. Different strategies were applied to select putative CNVs associated with CRC risk. The CNVs will firstly be verified for their existence by real-time PCR. Afterwards, the association of the respective CNVs with CRC susceptibility will be tested via MassArray for verification in a second case-control set. This study is being done in collaboration with the German HNPCC Consortium and the NGFN Plus CCN Group

Systematic dissection of Wnt signaling networks

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Wnt signaling pathways are of crucial importance during development and disease. The best characterized "canonical" Wnt pathway regulates the stabilization of beta-catenin and is highly conserved during evolution. Pathway components have been found to be mutated in melanomas, mammary, colorectal and other cancers. These disease-causing mutations lead to the inappropriate stabilization of beta-catenin and subsequent expression of oncogenic transcriptional targets. Several components of the Wnt pathway are promising targets for drug development.

We are using cross-species functional screening approaches to identify key factors that are required for the regulation of Wnt signaling networks. We initially screened the Drosophila genome by RNAi for conserved factors. In such a screen, we identified a novel multi-pass transmembrane protein, Evi/Wls, which is required for Wnt signaling in model organisms and human (Bartscherer et al., Cell 2006). Such functional RNAi screens have been expanded to human cancer cells and several large-scale RNAi screens have been completed. Here, we will present new approaches to perform genetic epistasis analysis and the computational methods to predict of topologies of Wnt signaling networks. Integration of functional screens with genome-wide association data sets will be used to predict disease-relevant candidate genes.

NGFN-Plus IG: MHC haplotype sequencing: An integrated approach to common disease

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The main focus of this project is the human major histocompatibility complex (MHC), the most important genetic region in relation to common diseases including inflammatory, infectious and autoimmune diseases as well as transplant medicine. Major national and international networks have now demonstrated associations between the MHC and numerous disease phenotypes of interest. To track down the disease genes, it is essential to identify 'candidate causal variations' in the regions of association. The complex nature of the MHC poses particular challenges: structural variation given by copy-number variations, insertions, deletions and inversions coupled with unprecedented levels of SNPs and differing degrees of recombination and LD, potentially extending over several Megabases. Direct MHC sequencing is the strategy of choice to resolve such complexity. The potential of this approach has already been demonstrated by sequencing a small number of MHC haplotypes (Horton et al., 2008).

Our major goal is to sequence disease-associated MHC haplotypes of interest to the NGFN at greater depth, on the population level. The scope and scale make a centralized effort both desirable and efficient. Competitive advantages are based on key resources and technologies: a) a world-wide unique haploid reference resource, fosmid libraries from 100 individuals of a representative German population cohort (200 haploid genomes); b) presence of a broad spectrum of risk MHC haplotypes confirmed by four-digit HLA-typing; c) availability of genotypic data (Affy 1000K), essential to mapping the clones into haplotypes; d) availability of a next generation sequencing platform to guarantee required capacity. In the first phase of this project, we have now identified MHC haplotype informative fosmids in our libraries by application of MHC SNP mapping panels and, based on these results, selectively isolated (Dapprich et al., 2008) first MHC clones from the haploid pools.

Identification of modifiers of intestinal tumor formation and progression using mouse B6/PWD chromosome substitution strains

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The individual genetic background is known to have a major effect on the life-time risk of developing cancer, and on cancer progression. The genetics of cancer susceptibility are however complex (polygenic), and thus it is almost impossible to assess the influence of the individual genetic background of humans on the lifetime risk of developing this disease. Mice share 99% of genes with humans, and also share common diseases. In particular, similar mutations cause colon cancer in mice and humans, and mouse models of human colon carcinogenesis are available (for instance APC-Min mice). Furthermore it is known that the genetic background of mice influences tumor multiplicity and the spectrum of organs affected.

The IG „Modifiers" seeks to unravel key genetic modifiers of colon cancer initiation and progression, using chromosome substitution strains (CSS) of the mouse and ultrahigh-throughput sequencing (Solexa), allowing us to enter a new dimension of the genetic analysis of cancer. We expect to isolate multiple genetic traits affecting cancer initiation, progression and recurrence, which will allow to define low- and high-risk groups among patients, and adapt treatment and follow-up regimes accordingly.

We show here first results of our APC-min/CSS screen for modifiers of intestinal tumor development, and present a novel genetic mouse model for modifier validation.

A genome-wide association study in major depression reveals association of SNPs on chromosome 12q21.3

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Objective: Major Depression is a common psychiatric disorder with a high heritability. However, several initial reports concerning susceptibility genes could not be confirmed unambiguously by subsequent studies or in meta-analyses.

Methods: We performed a genome-wide association study and subsequent replication in a combined sample of 1,271 depressed patients and 1,388 healthy controls.

Results and discussion: We identified and replicated the association of variants on chromosome 12q21.31 with Major Depression. These SNPs lie in an intergenic region flanked by the genes SLC6A15 and TMTC2. Genotype-dependent differences in mRNA expression levels in lymphoblastoid cell-lines of SLC6A15 but not TMTC2 were observed, with lower SLC6A15 expression in risk allele carriers. In a mouse model of chronic social stress SLC6A15 mRNA levels were decreased in the hippocampus of stress susceptible animals. Our results provide strong evidence for a role of SLC6A15 in the susceptibility for Major Depression.

Variations in tryptophan hydroxylase 2 leading to decreased serotonergic activity are associated with elevated risk for metabolic syndrome in depression

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Several studies have reported a strong comorbidity of major depression and metabolic diseases. Serotonergic neurotransmission has been shown to be involved in the pathophysiology of both depression and metabolic disorders contributing to metabolic syndrome. The rate limiting enzyme for serotonin biosynthesis in the central nervous system, tryptophan hydroxylase 2 (TPH2) is a strong candidate for both disorders. We investigated in an association study using a split-sample design whether genetic variants in TPH2 may contribute to the increased prevalence of metabolic syndrome in 988 subjects with a history of recurrent unipolar depression and 1023 psychiatric healthy controls of Caucasian origin. Diagnosis of recurrent unipolar depression was ascertained with the WHO SCAN-Interview. Prevalence of the metabolic syndrome was defined according to the IDF criteria. 41 Single Nucleotide Polymorphisms fully covering the TPH2 gene region were genotyped. Two polymorphisms (rs11179002 and rs17110690) showed significant associations with metabolic syndrome in patients with recurrent unipolar depression after correction for age, gender and multiple testing in stage one (300 patients / 300 controls). The association result of rs17110690 could be replicated in in stage two (688 patients / 723 controls). Risk-genotypes and risk-haplotypes for metabolic syndrome could be linked to lower TPH2 mRNA expression and lower CSF 5-HIAA levels previously reported in functional studies. Our findings suggest that TPH2 polymorphisms characterize a subgroup of depressed patients who are especially prone to develop metabolic disorders. We postulate that a genotype dependent impairment of serotonergic neurotransmission is involved in this gene-disease interaction. Identifying depressed patients at high risk for MetS using genetic variants could have direct clinical impact on individualized disease management and prevention strategies.

Identification of QTLs influencing anxiety and depression in mice

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In this study, we have mapped genetic loci, which are involved in the control of anxiety and stress-related behavior. In the first phase, we tested the behavioral sensitivity of 543 F2 animals from an intercross of C57BL/6J and C3H/HeJ mouse strains in four different models of stress: The zero maze, the light-dark and the startle response test are widely used models of anxiety, while the forced swimming test is a model of depression. The parental strains are located on distant branches of the mouse family tree, thus ensuring a high degree of genetic and stress-related behavioral variance. In the second phase, we genotyped the animals with 269 microsatellite markers with a mean distance of 5,56 cM and a Quantitative Trait Loci (QTL) analysis was carried out using the program R/QTL. We could identify QTLs on several chromosomes (1, 5, 7, 12, 15, 16, 17). Chromosome 5 contained multiple overlapping loci. Interestingly, several studies of anxiety and panic disorders in humans have identified a susceptibility region on chromosome 4, which is syntenic to our QTL region on chromosome 5. Comparison of human and mouse data, thus narrowed the candidate region to 14 Mb. A database search provided 109 annotated genes in this area. Potential candidate genes will be discussed.

Single nucleotide polymorphism associations with Type-D personality in the general population; findings from the KORA K-500-substudy

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Background: Individuals typically experiencing a combination of negative affectivity and social inhibition qualify for being Type-D personalities, which is considered to be a heritable construct. Type-D is relevant as an independent prognostic risk factor for cardiovascular disease. While genetic associations with many psychological traits are now well described, this information is not yet available for the Type-D personality.

Methods: A genome wide association study (GWAS) , the KORA (Kooperative Gesundheitsforschung in der Region Augsburg) F3 500K study, was performed in a representative, genetically defined population where over 300,000 single nucleotide polymorphisms (SNPs) were screened for associations with Type-D. SNPs with P-values □0.00015 (n=120) were considered for associations with Type-D phenotyped individuals.

Results: Of 1405 adults, 27.7% were classified with Type-D. Both SNPs and clusters of SNPs in specific gene regions were identified as contributing factors for Type-D. Of the 39 most significant SNP associations, many occurred in or near genetic regions important for immune function and neuronal plasticity such as endo/exocytosis, intracellular signaling, cytoskeletal organization and cellular adhesion. Additionally, seven genetic loci were identified that also have reported associations with bipolar disorder, autism, chronic fatigue, hypertension, diabetes and inflammation; an indication that common pathways may be involved in several psycho-somatic pathologies.

Conclusions: The observed SNP associations with a Type-D status support an underlying genetic propensity for Type-D personality. Novel genetic associations in Type-D populations may improve our understanding of the molecular pathways that trigger prevalent psychological traits that contribute to health burden.

Systematic investigation of the molecular causes of major mood disorders and schizophrenia (MooDS): SP3: Genomics of schizophrenia

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The aims of the project is to establish an in-depth understanding of the causative molecular mechanisms underlying the development of common psychiatric diseases such as bipolar disorder (manic depressive illness, BPD), unipolar disorder (major depression, UPD), and schizophrenia (SCZ).

Schizophrenia (SCZ) is a common mental disorder, affecting 0,5-1% of the population. Its direct costs in western countries range between 1.6-2.6% of total health care expenditures which account for 7-12% of the gross national product, and is the seventh most costly medical illness to western societies.

This subproject "SP3" will identify and functionally characterize genes involved in the development of SCZ following the same strategy proposed for bipolar and unipolar disorder (SP1 and 2) including genome wide association studies and finemapping.

1,500 SCZ patients, 2,400 population-based controls and further 1000 SCZ patients will be included into the study.

First results from this genotyping will be presented and discussed in comparison to genotyping results coming from the other two subprojects on bipolar disorder (manic depressive illness, BPD) and unipolar disorder (major depression, UPD).

No evidence for DUP25 in anxiety patients, as judged by molecular karyotyping

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Whole genome genotyping microarray chips are primarily designed for reliable high throughput genotyping of single nucleotide polymorphisms (SNPs). In SNP assays in use in our laboratory, the two SNP alleles are labeled with different fluorochromes. Fluorescence intensities of incorporated dye are quantitated after laser excitation. Measured fluorescence signals are reflecting the dosage of the respective SNP detection sequence in the genome. The more copies, the more signal, and fewer copies yield less signal. Genotyping chips can be employed for detecting genomic structural rearrangements with a much higher resolution than microscopical karyotyping. The diagnosis of heterozygous or homozygous deletions can be made with much higher precision, pinpointing breakpoints in most cases to an inter-SNP sequence. A duplication rearrangement on chromosome 15, termed DUP25, was reported (Gratacos et al, Cell 106:367-379, 2001) but could never be replicated by classical cytogenetic methods. We analysed the Illumina 300k genotyping data of our patients affected by panic disorder (N=270) for this duplication. No evidence could be produced as to the presence of DUP25 rearrangement in the anxiety and panic patients, as well as in an even higher number of controls.

Gene-Gene interaction between APOA5 and USF1: Two candidate genes for the metabolic syndrome

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Objective: All over the world the metabolic syndrome, a major cluster of risk factors for cardiovascular diseases, shows increasing prevalence. Several studies have found associations of both apolipoprotein A5 (*APOA5*) gene variants and upstream stimulatory factor 1 (*USF1*) gene variants with blood lipid levels and metabolic syndrome. USF1 is a transcription factor for *APOA5*.

Methods: We investigated a possible gene-gene interaction between these two genes on the risk of having the metabolic syndrome, using data from the German population-based KORA S4 survey (1,622 men and women aged 55-74 years). Ten *APOA5* single nucleotide polymorphisms (SNPs) were analyzed in combination with eight *USF1* SNPs. Interactions were assessed with logistic regression in an additive model adjusting for age and sex. For assessing the metabolic syndrome, we used the definition from the National Cholesterol Education Program's Adult Treatment Panel III (NCEP (AIII)).

Results: The overall prevalence for metabolic syndrome was 41%. Three SNP combinations showed a significant gene-gene interaction in the study population, each associated with a lower risk for metabolic syndrome (significance with p values between 0.024 and 0.047). Odds ratios were in a range between 0.33 (CI=0.13-0.83) and 0.40 (CI=0.15-1.12), each SNP with both minor alleles in homozygous states.

Conclusion: Thus, there is an indication of a gene-gene interaction between *APOA5* and *USF1* on the risk of having the metabolic syndrome.

Gastric inhibitory polypeptide receptor: Association analyses of several polymorphisms in large study groups pertaining to obesity

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Aims: Gastric inhibitory polypeptide (GIP) has been postulated to be involved in type 2 diabetes mellitus and obesity and exerts its function through its specific receptor, GIPR. We genotyped four *GIPR* SNPs (rs8111428, rs2302382, rs1800437 and rs11672660) in German families with ate least one obese index patient, two case-control studies and two cross-sectional population-based studies.

Methods: Genotyping of a non-synonymous SNP (rs1800437), an intronic SNP (rs2302382), and a SNP in the putative promoter region (rs8111428) was performed by MALDI-TOF, ARMS-PCR and RFLP. The family-study: 761 German families with at least one extremely obese child or adolescent (n = 1,041) and both parents (n = 1,522).

Case-control study: (a) German obese children (n = 333) and (b) obese adults (n = 987) in comparison to 588 adult lean controls. The two cross-sectional population-based studies (KORA (n = 8,269) and SHIP (n = 4,310)).

Results: We detected over-transmission of the A-allele of rs2302382 in the German families (nominal $p_{TDT\text{-}Test}$ = 0.0089). In the combined case-control sample, a similar genetic effect was observed with an estimated OR of 1.55 (95% CI 1.10; 2.20, nominal $p_{CA\text{-}Test}$ = 0.013) for the joint obese group homozygous for the rs2302382 A-allele compared to CC carriers. A similar trend was also found in KORA where the rs2302382 A-allele led to an increase of 0.12 BMI units (95% CI -0.04 - 0.28, nominal p = 0.136). In SHIP, however, the A-allele of rs2302382 was estimated to contribute an average decrease of 0.27 BMI units (95% CI -0.52; -0.24; nominal p-value = 0.031).

Conclusions: Our data suggest the potential importance of *GIPR* variants for obesity. However, additional studies are warranted in light of the conflicting results obtained in one of the two population-based studies.

Genetic variation in the Resistin locus and components of the metabolic syndrome in 5100 subjects

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Obesity and related conditions such as insulin resistance, type 2 diabetes, hyperlipidaemia, and hypertension are influenced by resistin expression and secretion. Thus, the Resistin gene (*RETN)* is a candidate gene for certain risk factors, which cluster in the metabolic syndrome. Therefore, we analysed the association between single nucleotide polymorphisms (SNPs) of the human *RETN* and metabolic syndrome, as well as related parameters. The analysed population-representative sample comprised 1462 subjects from the German KORA Study. The SAPHIR study and a sample from Utah were used for replication. Genotyping was carried out by matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) analysis of allele-dependent primer extension products. We found no association of *RETN* SNPs with the metabolic syndrome, or type 2 diabetes. Among the single components of the metabolic syndrome, a statistically significant difference between the genotype groups was observed for the *RETN* SNP rs3760678 with triglyceride levels (p=0.0003). Although this finding was inconsistent in the single samples, we have shown significantly decreased triglyceride levels for rs3760678 minor allele carriers in combined analysis (5100 subjects) for the first time. However, the functionality of this genetic variant has to be clarified. Our results may support the role of resistin in lipid metabolism with differences between normal and obese subjects.

Planning genome wide association studies under limited budget

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Genome-wide association studies should be sufficiently powered to detect single variants which make small or moderate contributions to diseases risk. For example, 15.000 individuals (cases + controls) are necessary to detect a variant with population frequency of 10% which causes a 25% increased risk of disease (OR=1.25) in a screening study using a 1000k SNP chip. Genotyping would cost about 4.5 Mio$. However, study budgets are limited. This raises the question of optimal allocation of the money. In the above example, if the grant was 2.25 Mio$, what should I do? If I decide to run the 1000k chip in half of the sample, the power will drop from 80% to 20%!

We have developed multi-stage designs which maximize the power of the study under budget constraints. In multi-stage designs, the marker set is gradually focussed on promising markers, dropping the large number of null markers as early as possible. With a multi-stage design optimally fitted to the individual study, in many situations it may be possible to keep the study power nearly at the full level even when the available budget for genotyping is halved (Pahl 2008). It is also possible to take recruitment costs into consideration and to minimize overall study costs while keeping the study power constant at, say, 80% (Müller 2007). Further progress was recently achieved through the development of so-called *flexible designs* (Scherag 2008), where all interim data such as odds ratios, allele frequencies, and external information can be used for interim marker selection. Chip sizes are increasing, and highly expensive whole sequence association studies are in sight. Flexible and multi-stage designs may reduce costs and make studies feasible. We offer a 10 minutes *oral presentation* for statistical non-specialists.

References: Müller H-H et al. (2007) Genetic Epidemiology 31:844-852
Pahl R et al. (2008) Biostatistics. Accepted.
Scherag A et al. (2008) Biometrics. Accepted.

Large family-based genome-wide association scan for early onset extreme obesity

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Aims: Although heritability for obesity is substantial, the underlying genetic mechanisms are not well understood. We have performed the to our knowledge first family-based genome wide association study (GWA) for early onset (extreme) obesity.

Methods: a) GWA (1000k; Genome-Wide Human SNP Array 6.0 comprising 906,600 single nucleotide polymorphisms) for early onset extreme obesity based on 424 extremely obese young German individuals and both of their parents; transmission disequilibrium tests;

b) for confirmation we analysed already available 1000k GWA data on 453 extremely obese children and adolescents (cases) and 435 healthy controls.

Results: Single nucleotide polymorphisms (SNPs) in a novel candidate gene for obesity on chromosome 8 rendered the lowest p-value (nominal p= $1x10^{-6}$). Surprisingly, the previously described SNPs in the fat mass and obesity related gene (*FTO)* and the melanocortin 4 receptor gene (*MC4R)* gene were not among the best 100 SNPs. The best 20 SNPs of the combined approach (TDT and cases and controls) will be followed up in >20,000 individuals of central European origin of which >2,000 are children and adolescents.

Conclusions: This first family-based GWA for extreme early onset obesity identified variation in a novel candidate gene for obesity. Confirmatory analyses are currently pursued. Parent of origin effects are currently being assessed.

The premature nonsense mutation W16X in the melanocortin-4-receptor gene causes obesity in mice

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The Melanocortin-4-Receptor (MC4R) is a G-protein coupled receptor that is widely distributed throughout the brain. Activation of MC4R by pro-opimelanocortin derived peptides like alpha-melanocyte stimulating hormone (MSH) causes promotion of negative energy balance. In humans, 6% of obese people encode polymorphisms in the MC4R gene.The point mutation W16X is one of 5 known nonsense mutations in the human MC4R gene and is positively associated with obesity.Our in vitro analysis revealed that the W16X variant has a loss-of-function phenotype characterized by reduced plasma membrane expression and impaired cyclo AMP accumulation. Incubation of cell cultures with the aminoglycoside G-418 partially restored the mutant phenotype of W16X due to the ability of aminoglycosides to suppress specifically premature stop codons.Furthermore we generated a Mc4r-X16 knock-in mouse line by homologous recombination in embryonic stem cells. Metabolic phenotyping demonstrated that knock-in mice are obese, hyperphagic and longer, resembling the same characteristics of Mc4r null mice. In a next step we aim to rescue the obese phenotype of knock-in mice by administration of aminoglycosides like gentamicin or amikacin in vivo.

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NGFN^{PLUS}-Network "molecular mechanisms in obesity"

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The major scientific goal of our network is the identification of genes/alleles predisposing to obesity and their subsequent evaluation in epidemiological, developmental, clinical, functional and therapeutic terms.

Genome wide association studies (GWA) are already leading to the identification of novel obesity genes; for this reason the extension and subsequent maintenance of our successful research pipeline established during NGFN1&2 are of utmost importance. Using GWA data based on more than 4,000 subjects - (including data of 487 extremely obese and 442 healthy lean individuals and 424 'obesity trios') - we have already identified novel polygenes (e.g. Loos et al., 2008, Nat Genet; Willer et al., Nat Genet, *in press*); additionally studies (e.g. combined analyses, parent of origin effects) are currently pursued.

Our recent studies in recombinant congenic mice showed that a mutation in *Tbc1d1* suppresses high-fat diet-induced obesity by increased lipid use in skeletal muscle (Chadt et al., 2008, Nat Genet). We will assess the role of this gene in human body weight regulation.

The relevance of alleles detected by GWAs or animal models will be estimated in relationship to different developmental stages in epidemiological samples. Functional studies will focus on the implications of the detected genetic variation using *in vitro* and *in vivo* models. The analysis of *Fto* knock out mice will facilitate the analysis of this important obesity polygene.
Additionally, we address implications of molecular findings for the treatment of obesity. We will initiate systemic studies using *in vivo* models to examine side effects of therapeutically induced weight loss at both the systemic and molecular level.

Obesity relevant melanocortin-4-receptor gene variants and identity by descent: Analysis of single nucleotide polymorphisms - not only in the context of association studies

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The melanocortin-4-receptor (MC4R) plays an important role in the hypothalamic regulation of body weight. Currently, mutations in the MC4R gene are the most common genetic cause for obesity.The most frequent variant is the stop mutation Y35X always appearing as a haplotype in association with the variant D37V. Furthermore, there are two more variants with a relatively high frequency: The variant V103I, presumed to be protective against obesity and carried by 2% of the population, and the variant S127L causing partial loss of function. The incidence of two mutations on the same allele indicates a founder effect. In rare cases we identified the variants V103I and S127L on the same allele in obese patients. In order to examine whether these double mutations occur spontaneously or are based on heredity transmission, we analysed single nucleotide polymorphisms (SNPs) within a range of about 240kb around the MC4R gene in order to create haplotypes. The minimum of heterozygosity in the database was 40%. Our sample group consisted of a healthy control group and, in order to establish haplotypes from trios, of normal weight and obese patients. Recently, during a genome-wide association study designed to identify new obesity relevant candidate genes, a SNP (rs17782313) was identified 188kb downstream of the MC4R gene indicating to be highly associated with obesity. The functional relevance is still unclear. Analyses of this SNP in our control group show also a high significance of association with obesity (p=0.01). The evaluation of the collected data will show whether the double mutations are due to a common ancestry or occur spontaneously. In addition we will get information if rs1778213 shows linkage disequilibrium with other SNPs, occurring in the immediate region of the MC4R gene.

Novel genetic variants for obesity identified in a joint analysis of two genome-wide association scans for early onset extreme

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Aims: Genome-wide association studies (GWAS) have successfully contributed to the detection of robustly associated genetic variants involved in obesity-related traits. In our studies we aimed at detecting more of such robustly associated genetic variants.

Methods: First, we jointly analysed two GWAS with >2,000 individuals of central European origin which both focus on extremely obese children and adolescents. Secondly, we followed up our findings in >20,000 individuals of central European origin of whom >2,000 were children and adolescents. **Results:** We found that genetic variants related to the fat mass and obesity related gene (*FTO)* and the melanocortin 4 receptor gene (*MC4R)* gene were again strongly associated with obesity. Moreover, we identified new variants not previously reported to be related to early onset obesity. By investigating nuclear families as well as obese and unselected individuals, we show that our findings are consistent across all follow-up samples.

Conclusions: Functional studies of the implied regions may contribute to new biological insights for the development of obesity and related disorders such as cardiovascular disease and diabetes.

Proteomic profiling of mouse hypothalamus in strains susceptible or resistant to diet-induced obesity

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Obesity has emerged to a worldwide public health problem. It is caused by a complex disorder of appetite regulation and energy metabolism which are controlled by multiple factors such as life style, genetic predisposition and diet. The high-fat western-type diet is one of the major factors promoting the development of obesity. However, not all of the high-fat diet consumers become obese.

The responsible peptidergic determinates within central energy balance controlling centres of the brain are not fully understood. In this study, three different inbred mouse strains - AKR/J, SWR/J and CB57BL/6N were either fed a high-fat or standard chow diet for ten days. The AKR/J strain represents a mouse model for diet-induced obesity (DIO), as mice of this strain developed obesity when fed a high fat diet. In contrast, mice of the SWR/J strain are resistant to DIO and show no increase in body weight following a high fat diet as compared to standard chow. Body weight development of CB57BL/6N mice is intermediate with respect to DIO.

We sampled hypothalami with neuroanatomical precision of each strain/diet group (n=5-6/per group) and then applied 2-D Fluorescence Difference Gel Electrophoresis (2-D DIGE), a method that labels protein samples with fluorescent dyes before 2-D electrophoresis. We accurately analysed and quantified differences in hypothalamic protein abundance in response to DIO. Our experimental approach will help to understand, to what extend changes in the hypothalamic proteome may be associated with the increase in body fat mass in obese mice.

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Nob3 - A major QTL for obesity on mouse chromosome 1

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Objectives: Several chromosomal regions (quantitative trait loci, QTL) and gene variants (*Tbc1d1*, *Abcg1*, *Nmur2*, *Niddm1*) associated with different degrees of obesity and related metabolic disorders were previously identified by our group with outcross populations derived from the New Zealand obese (NZO) mouse. A major obesity QTL (*Nob3*) was identified on distal mouse chromosome 1 (LOD score 12.7) which was responsible for a body weight increment of approximately 12 g at week 22.

Methods: Via successive backcrossing the obesity QTL *Nob3* was transferred to the C57BL/6 background. Thereby, mice carrying different fragments of the locus on chromosome 1 were generated and a detailed phenotypical characterization (body weight, body fat distribution) has been performed over a time period of 20 weeks to define a minimal chromosomal segment of the QTL *Nob3* which contains the disease gene.

Results: In the 3rd backcross generation (N3) heterozygous *Nob3* allele carriers developed a significantly higher body weight than homozygous carriers of the B6 allele (23.7 ± 0.3 g vs. 27.0 ± 0.4 g; means ± SEM, p< 1E-08, wk.22), resulting from an increased lean mass (17.1 ± 0.2 g vs. 19.0 ± 0.2 g; means ± SEM, p< 4E-08, wk.22). Up to now, several recombinant congenic strains carrying 5-50 Mbp of the QTL *Nob3* were generated and characterized for their body development. By the analyses of these recombinant lines the minimal critical fragment was identified with the RCS-VI (22.3 ± 0.2 g vs. 23.9 ± 0.3 g; means ± SEM, p< 4E-05, wk.22), which allows us to reduce the susceptibility region from approx. 50 to 10 cM and the number of genes from 780 to 160 genes.

Conclusion: This result represents conclusive evidence for an adipogenic allele in this locus, and indicates that the interval-specific congenic introgression is the preferable strategy for positional cloning of the gene.

The fat-mass and obesity associated (FTO) rs9939609 single nucleotide polymorphism is associated with high C-reactive protein levels independently from obesity indices in EPIC-Potsdam

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Of all inflammatory markers studied so far, C-reactive protein (CRP) has been shown to be most consistently associated with cardiovascular risk. Adipose tissue is a key factor determining C-reactive protein (CRP) plasma levels. Variants of the fat-mass and obesity-associated (*FTO*) gene have been identified as determinants of human obesity in the recent past. We used a population-based sample of 2,415 participants from the large prospective European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort study to investigate whether the *FTO* rs9939609 T>A single nucleotide polymorphism might alter CRP levels. The analysis revealed a significant association of the A-allele with hs-CRP levels in both genders. Each copy of the *FTO* rs9939609 A-allele was associated with 21 % higher plasma CRP levels (*P*=0.002) in men and 14 % higher levels (*P*=0.01) in women. The association was attenuated, but remained statistically significant after additional adjustment for body mass index, waist-to-hip ratio, and other potential confounding factors (men, +14 %, *P*=0.03; women, +12 %, *P*=0.02; per A-allele). Similar results were obtained when subjects with CRP levels higher then 10 mg/L were excluded. Our data provide first evidence that the *FTO* rs9939609 polymorphism contributes to basal plasma CRP levels independently of obesity indices.

MicroRNAs in the pathogenesis of neuroblastoma

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Neuroblastoma is the most common extracranial childhood tumor comprising cases with spontaneous regression as well as rapid disease progression despite aggressive therapy. *MYCN* amplification is a common feature of aggressive tumor biology in neuroblastoma. The MYCN transcription factor has been demonstrated to induce or repress expression of numerous genes. MicroRNAs (miRNA) are a recently discovered class of short RNAs that repress translation and promote mRNA degradation by sequence-specific interaction with mRNA. We identified seven miRNAs that are induced by MYCN *in vitro* and are upregulated in primary neuroblastomas with *MYCN* amplification. Three of the seven miRNAs belong to miR-17 cluster, that has previously been shown to be regulated by c-Myc. The miR-17-92 polycistron acts as an oncogene in hematopoietic progenitor cells. We show here that miR-221 is also induced by MYCN in neuroblastoma. Previous studies have reported miR-221 to be overexpressed in several other cancer entities, but its regulation has not yet been associated with Myc. For further functional analysis, we conditionally overexpressed or knocked-down miR-17-92 and miR-221 in neuroblastoma cell lines. We subsequently use the Amersham DIGE System to identify miRNA target genes using high-throughput proteomic analysis. In addition, transgenic mice conditionally overexpressing or lacking miR-221/222 were generated and are now being analyzed to characterize miRNA function *in vivo*. Crossbreeding these mice with mice engineered to develop spontaneous neuroblastomas will reveal the contribution of miR-221/222 to neuroblastoma pathogenesis *in vivo*.

Heterozygous ATP13A2 variants in patients with early-onset Parkinson disease and controls

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Parkinson disease (PD) is a common neurodegenerative disorder characterized by bradykinesia, resting tremor, rigidity, and postural instability. Four genes responsible for recessively inherited forms of PD have been identified, including the recently discovered ATP13A2 (PARK9) gene. The gene encodes a lysosomal P-type ATPase and carriers of two mutated alleles often present with atypical PD (Kufor Rakeb syndrome).

To evaluate the role of ATP13A2 mutations in PD, we screened all 29 coding exons of ATP13A2 in 112 mostly European patients (16 juvenile parkinsonism, 96 early-onset PD) and 55 neurologically healthy German controls by sequencing and dHPLC. Also, 200 chromosomes from healthy individuals were tested for the detected alterations.

None of the tested individuals carried homozygous or compound heterozygous ATP13A2 mutations. Among the 112 patients, we identified six carriers (5.4%) of six different heterozygous nonsynonymous variants in ATP13A2. One of these changes was also present in one of 200 specifically tested control chromosomes. Among the 55 sequenced controls, we detected a synonymous and a nonsynonymous variant. The latter one was also found in one patient. Interestingly, among the four patients with nonsynonymous variants not present in controls, one carrier also harbors two mutations in the Parkin gene. Clinically, none of the carriers had atypical features previously described in patients with two mutated ATP13A2 alleles. Transcranial ultrasound in two affected carriers revealed typical hyperechogenicity of the substantia nigra; voxel- and region-of-interest-based morphometry showed mild atrophy in selected areas of the brain.

Our data suggests that homozygous or compound heterozygous mutations in the ATP13A2 gene are not a common cause of PD. However, heterozygous variants are present in a considerable number of patients but are - based on this relatively small sample size - not significantly more frequent in patients compared to controls.

Interactions of viral and cellular miRNAs in the MCMV system

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Viral miRNAs not only modulate the host environment, but interact with the host miRNA and siRNA pathways as well. Since RNAi is an ancient antiviral response pathway, viral miRNAs can either down-regulate the expression of host miRNA/siRNA biogenesis factors, or simply outcompete the cellular small RNAs for effector proteins. It has been shown that association of specific small RNAs with their RISC-complex is conferred by proteins of the argonaute-family, and in the Drosophila system the sorting mechanism distinguishing between the miRNA and siRNA pathways has already been identified.

Murine cytomegalovirus (MCMV) infection of NIH3T3 fibroblasts leads to expression of a large amount of viral miRNAs. We therefore chose this system to answer the question of whether virus-derived small RNAs function as competitive inhibitors. To this end, sorting of prominent cellular and viral miRNAs into RISC-complexes was investigated.

One strategy is to use the cellular miRNAs let7 and miR16 as well as the abundant viral miRNAs m01-4 and M23-2 in miRNA-Pullout assays followed by western blot analysis against specific argonaute proteins. Thus, preferences of the argonaute proteins for either cellular or viral miRNAs could be analyzed.

Furthermore, the amounts of the chosen miRNAs over the time course of viral infection were quantified by qPCR. As expected, viral miRNAs increased over time. As no reduction of the cellular miRNAs could be observed, viral infection apparently does not impair cellular miRNA biogenesis per se.

Sample preparation for an integrated analysis of genomic, transcriptomic, and proteomic markers from the same tissue source

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Molecular tumor markers can be identified by diverse high throughput technologies. However, due to insufficient amount or quality of tissue samples as well as tumor heterogeneity, the generation of different sets of molecular data from the same physical sample has remained a challenge. This is particular crucial if integration of data in a systems biology manner is intended.

The aim of this work was to provide a standardized procedure for the isolation of different molecular substance classes from the same clinical sample. RNAlater-preserved tissue samples from patients who had undergone radical prostatectomy were cryosected into 20-40 slices, and representative sections were histopathologically characterized. Prostate tumor regions were macrodissected from the remaining sections, pooled, and used for the extraction of high-quality genomic DNA, total RNA, micro RNA and protein. We show that these samples can be successfully subjected to the projected analyses of the integrated analyses in the IG Prostate Cancer, including exon-level transcriptional profiling, microRNA profiling, mutation and methylation analysis of genomic DNA, as well as protein analysis using reverse-phase protein arrays and 2D-gel electrophoresis. Comprehensive datasets will be interrogated and combined to elucidate molecular signatures with strong associations to important clinical parameters in prostate cancer.

Systematic full resequencing of patient populations to assess genetic susceptibility in complex diseases

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SNP-based genome wide association scans (GWAS) have identified multiple susceptibility genes and loci in several complex diseases. Many identified associations are highly replicable in different patient populations but causative variants and mechanisms often remain unknown. It appears that rare SNPs but also intronic variants and non-SNP based variants play an important role to explain disease pathogenesis. Moreover, power of GWAS is low and many associations in the primary analysis that may represent "true" findings are not selected for replication in these experiments.

"Next generation sequencing" offers a new technology to solve these problems. The DISSEQ consortium of the NGFN will conduct prototypic experiments in Alzheimer, Crohn disease and diabetes. Both systematic full re-sequencing and targeted re-sequencing of loci will be conducted. Sequence variants with putative mechanistic function that are identified by sequencing will be examined for association and replication in large NGFN and international samples with thousands of patients and controls through other technologies (e.g. SNP genotyping).

DISSEQ will become part of the larger EUVADIS consortium where it will represent the interests of the NGFN.

The first full Crohn patient genomes and transcriptomes were analyzed and will be presented during the NGFN meeting.

www.disseq.org

Systematic detection of genetic variation associated with exceptional life expectancy in humans

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Life expectancy in humans is influenced by various environmental and genetic factors. Until recently, only variation in the apolipoprotein E gene (*APOE*) was found to be consistently associated with life expectancy in various populations. In September 2008, Willcox et al. published a study describing the association of variation in the *FOXO3A* gene with human longevity. FOXO3A is an evolutionarily conserved key regulator of the insulin-IGF1 signaling pathway. However, the Willcox' results were tentative as they had not been replicated in an independent population. Therefore, we have investigated 16 known *FOXO3A* SNPs in our extensive collection of 1762 German centenarians/nonagenarians and younger controls. Our results provide conclusive evidence that polymorphisms in this gene are indeed associated with the ability to attain exceptional old age. Replication in a French centenarian sample generated a trend that supported our findings. Furthermore, we observed that the *FOXO3A* association was considerably stronger in centenarians than in nonagenarians, highlighting the importance of the oldest old for genetic longevity research. Besides, we have identified and confirmed the DNA repair gene *OLD1** as a novel susceptibility factor for exceptional life expectancy in centenarians. Detailed genetic and functional analyses have revealed a hitherto undescribed role for the helix-loop-helix transcription factor TFX* as a negative regulator of *OLD1* transcription. Moreover, we have identified an *OLD1* promoter variant that can counteract the TFX-mediated repression of the gene, which in turn promotes genomic integrity and survival to exceptional old age. Our finding renders *OLD1* the third confirmed gene to affect late-life survival after *APOE* and *FOXO3A*. Further longevity candidates are being investigated in a genome-wide case-control association study using Affymetrix Genome-Wide Human SNP Arrays 6.0 (906,600 SNPs).

*Gene names have been masked due to publication reasons

Analysis of gene-gene interaction within the filaggrin pathway

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Filaggrin is a key protein for the development of the cornified envelope and its deficiency due to null mutations in the *FLG* gene has been firmly established as risk factor for atopic eczema (AE). Processing of profilaggrin to biologically active filaggrin monomers involves several dephosphorylation and proteolytic steps, and their impairment might also disturb skin barrier function. Among the proteases suggested to be implicated in profilaggrin processing is the stratum corneum chymotryptic enzyme (SCCE), which is possibly regulated by the *SPINK5* -derived serine protease inhibitor LEKTI. An insertion in the 3´ untranslated region of the kallikrein 7 gene (*KLK7*) encoding SCCE as well as a *SPINK5* variant have been reported to be associated with AE, but have not been widely replicated.

In our study we aimed at clarifying the individual role of these genetic variants for AE, and, considering the potential biological interactions between filaggrin, SCCE and LEKTI, we also examined potential epistatic effects between these polymorphisms.

Association analysis was carried out in 486 German families as well as in a German and British/Irish case-control cohort (1191 cases vs 4544), followed by an additional study of the *SPINK5* polymorphism and the *FLG* mutations in 1583 eczema patients and 6063 controls from the Avon Longitudinal Study of Parents and Children cohort (ALSPAC).

Whereas the strong effect of *FLG* polymorphisms was confirmed, no association of the *KLK7* insertion and the *SPINK5* polymorphism rs2303067 could be detected in the case-control analysis. However a weak association with maternal transmission was observed for the *SPINK5* variant in the family collection. There was no evidence for interaction between *FLG*, *KLK7*, and *SPINK5* variants that significantly increases AE risk. Thus, our data confirm the impact of filaggrin deficiency due to *FLG* loss-of-function mutations on AE risk, but do not support the hypothesis that this effect is dependent on *KLK7* or *SPINK5*.

Clinical impact of defensin copy number variation

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One unexpected feature of the human genome is the high structural variability across individuals. Frequently, large regions of the genome show structural polymorphisms and many vary in their abundance (copy number variation, CNV).

The defensin (DEF) gene cluster at 8p23.1 is one of the best studied CNV regions due to its potential clinical relevance for innate immunity, inflammation and cancer. However, accurate methods for the characterization and typing of DEF copy number variations are needed.

We developed methods for the quantification of DEF copy numbers and proved strict concordance for the genes of the beta-defensin cluster. Absolute copy numbers ranged from two to nine for the beta-defensin cluster and zero to four for *DEFA3*. The CNV-typed samples, including some from HapMap, are publicly available and may serve as a universal reference for absolute copy-number determination [1].

Combination of the copy number quantification with PCR/cloning based haplotyping in a prostate cancer (PC) association study, investigating two independent patient cohorts and a control cohort showed that high copy numbers of the cluster are underrepresented in cancer patients and that four common *DEFB104* haplotypes are associated with the risk of sporadic PC [2].

Keywords: Copy Number Variation (CNV), Multiplex Ligation-dependent Probe Amplification, defensin, concordance, prostate cancer, association study

References:

[1] Groth, M. *et al.* Human Mutat. **2008** 29, 1247-1254

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A comprehensive evaluation of SNP genotype imputation

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Genome-wide association studies have contributed significantly to the genetic dissection of complex diseases. In order to increase the power of existing marker sets even further, methods have been proposed to predict individual genotypes at untyped loci from other marker sets by imputation, usually employing the HapMap data as a reference. Although various imputation algorithms have been used in practice already, a comprehensive evaluation and comparison of these approaches, using genome-wide SNP data from one and the same population, is still lacking. We therefore investigated four publicly available programs for genotype imputation using data from 449 German individuals genotyped in our laboratory for three genome-wide SNP sets. We observed that HapMap-based imputation in a Northern European population is powerful and reliable, even in highly variable genomic regions such as the extended MHC on chromosome 6p21. However, while genotype predictions were found to be highly accurate for all four programs, the number of SNPs for which imputation was actually carried out varied substantially.

Genetic variants in the transcription factors T-bet, HLX1 and GATA3 and their functional role in the development of asthma

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Introduction: The transcription factors T-bet, HLX1 and GATA3 play a crucial role in T cell commitment and asthma development. While T-bet and HLX1 induce the differentiation of Th1 and are able to block Th2 differentiation, GATA3 has the opposite effect. We speculated that genetic alterations in T-cell transcription factors may lead to a deregulation of the immune system and asthma.

Methods: Mutation screenings were performed for *T-bet*, *HLX1* and *GATA3* genes. Tagging SNPs were genotyped by MALDI-TOF MS in three cross-sectional study populations of German children from Munich, Dresden (ISAAC II) and Leipzig (total N=4,264) and nested asthma case-control populations thereof (ISAAC II, N=1,872). Asthma associated promoter SNPs in *T-bet* and *HLX1* were investigated by functional genomics.

Results: *T-bet* SNPs showed an increased asthma risk in the case-control analysis (T-1514C: OR 2.60, 95%CI 1.34-5.03; p=0.003; C9898T: OR 1.97 95%CI 1.18-3.30, p=0.009). For *HLX1*, two tagging SNPs were significantly associated with the development of asthma (C-1407T: OR 1.44, 95%CI 1.11-1.86, p=0.006; T346C: OR 0.73, 95%CI 0.56-0.95, p=0.017). Risk allele combinations increased the OR more than threefold (OR 3.39, 95%CI 1.11-10.42, p= 0.0327). In contrast, no effects were observed for *GATA3* SNPs. In functional studies, *T-bet* and *HLX1* promoter SNPs significantly influence gene expression *in vitro* and altered transcription factor binding.

Conclusions: Our data indicate that SNPs in the Th1 associated transcription factors T-bet and HLX1 significantly increase the risk for childhood asthma and alter gene expression levels. In contrast, polymorphisms in the Th2 associated transcription factor GATA3 have no influence on asthma development, suggesting that asthma may be a disease of lacking Th1 signals rather than a Th2 disease.

Genome-wide association study for atopic dermatitis

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Atopic dermatitis (AD) is a highly prevalent and strongly heritable inflammatory skin disease with complex etiology. We attempted to identify genetic variants conferring risk to AD by typing a genome-wide set of 440.794 SNPs in two independent German samples. Set 1 included 939 AD cases and 975 controls and Set 2 consisted of 270 affected-sib-pair AD families including 529 affected individuals. A set of 58 SNPs consistently associated to AD in both discovery sets was subsequently tested for replication in an independent sample of 1363 AD cases and 2739 controls (Set 3). Two previously unreported AD risk factors provided strong evidence for replication in Set 3 almost reaching genome-wide significance in an overall analysis (Marker 1 combined_p= 6.55×10^{-7}; Marker 2 combined_p= 1.27×10^{-6}). In both cases the associated SNPs were confined to a LD-block containing a single gene. Six additional loci including a number of biological candidate genes for AD were nominally replicated in Set 3 ($p< 0.05$) suggesting that they may also be involved in AD susceptibility. Additionally we provide evidence that, apart from previously reported Filaggrin mutations, additional risk factors for AD exist within the Epidermal Differentiation Cluster on 1q21 (marker 3 combined_p= 1.11×10^{-5}). In conclusion, we identified two new risk factors for AD and provide a set of novel candidate genes showing association with AD in 3 independent samples. Present data suggest that multiple low-risk genetic variants (OR< 1.5) influencing skin biology and immune responses contribute to AD susceptibility and that these effects may be efficiently detected through whole genome association.

Identification of ANXA11 as a novel risk locus for saroidosis by a genomewide association study

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Sarcoidosis is a systemic granulomatous inflammatory disorder with predominant manifestation in the lung. In the first genome-wide association study (GWAS; >440,000 SNPs 499 German patients, 490 controls) we found associations with BTNL2 and several HLA-loci. Moreover, we identified significant association with annexin A11 (ANXA11) on chromosome 10. Validation in an independent sample (1,649 cases, 1,832 controls) confirmed the association of ANXA11 (rs2789679, $P=3.0\times10^{-13}$; rs7091565, $P=1.0\times10^{-5}$). A common non-synonymous SNP (rs1049550, C>T, p.Arg230Cys) was found to be strongly associated with sarcoidosis. Additional risk variants in the region (rs1953600, rs2573346, rs2784773) and the GWAS lead SNP were in strong linkage disequilibrium with rs1049550. We could not find an association of rs1049550 with other granulomatous diseases (Crohn disease, Ulcerative colitis). ANXA11 has complex and essential functions in several essential biological pathways, including apoptosis and proliferation.

Allele-specific NF-kB-binding alters STAT6 expression and contributes to genetic IgE control

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Background: The IL-4/IL-13 pathway is central for IgE regulation. STAT6 is the major transcription factor within this pathway. STAT6 polymorphisms were recently associated with elevated total IgE levels in a Genome-Wide Association study.

Objective: This study aimed to assess biological mechanisms by which an IgE-associated genetic variation in STAT6 may potentially influence gene expression.

Methods: STAT6 intron 2 either carrying the wildtype C or the polymorphic T allele of the putatively causal SNP rs324011 was cloned into STAT6 promoter vectors to investigate their influence on gene expression by in vitro luciferase assays. Allele-specific STAT6 gene expression was studied ex vivo by Real-Time PCR in 239 individuals. Transcription factor binding depending on rs324011 was examined by Electrophoretic Mobility Shift Assays (EMSA) in Jurkat T-cells and primary CD4+ T-cells.

Results: STAT6 intron 2 acts as a silencer regulatory element in transient transfection experiments. The polymorphic T allele at rs324011 (in linkage disequilibrium with the Genome-Wide Association signal and consistently associated with elevated IgE levels in three previous studies) increases STAT6 gene expression significantly in vitro ($p < 0.00001$) and ex vivo ($p < 0.01$) compared to the wildtype C allele. These effects correlate with the creation of a novel, T allele-specific binding site for the transcription factor NF-kB in T-cells.

Conclusions: The consistently replicated effects of genetic variance in STAT6 on IgE regulation may in part be explained by allele-specific alterations in NF-kB binding at rs324011 and consecutive changes in STAT6 gene expression.

Sequence variants in IL10, ARPC2 and multiple other loci contribute to ulcerative colitis susceptibility

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Inflammatory bowel disease (IBD) manifests as either of two related subtypes, ulcerative colitis (UC) or Crohn disease (CD). Systematic identification of susceptibility genes for IBD has thus far focused mainly on CD, while little is known about the genetic architecture of UC. Here, we report on a genome-wide association study with 440,794 SNPs genotyped in 1167 UC patients and in 777 healthy controls. Twenty of the most significantly associated SNPs were tested for replication in three independent European case-control panels comprising a total of 1855 UC patients and 3091 controls. Among the four consistently replicated markers, SNP rs3024505 immediately flanking the interleukin 10 gene (*IL10*) on chromosome *1q32.1*, showed the most significant association in the combined verification samples (P=1.35×10^{-12}; OR=1.46 [1.31-1.62]). The other markers were located in *ARPC2* and the *HLA/BTNL2* region. Association between rs3024505 and CD (1848 cases, 1804 controls) was weak (P=0.013; OR=1.17 [1.01-1.34]). IL10 is an immunosuppressive cytokine that has long been proposed to influence IBD pathophysiology. Our findings strongly suggest that defective IL10 function is central for the pathogenesis of the UC subtype of IBD.

A GLUT1 mutation in patients with constant spastic paraplegia and paroxysmal dyskinesia

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Glut1 is the glucose transporter of the blood brain barrier, thus a crucial molecule to deliver the most important energy carrier to the brain. Mutations in Glut1 have been found in Glut1-deficiency syndrome, a severe syndrome of early childhood with drug resistant epilepsy, microcephaly and progressive mental retardation. Recently, we detected mutations in Glut1 in patients with paroxysmal exertion-induced dyskinesia. Auburger and colleaques described a family with paroxysmal dyskinesia in combination with constant spastic paraplegia in some patients and mild gait ataxia. The family included 18 affected family members and 11 unaffected probands. A linkage analysis found linkage close to the Glut1 locus on chromosome 1p (Genomcis 1996; 31:90-94). We now re-analyzed the family clinically, recruited more family members, and sequenced the Glut1 gene *SLC2A1*. We found a p.R212C missense mutation. Functional analysis of the mutation expressed in Xenopus laevis oocytes revealed a significant reduction of glucose uptake compared to the wildtype. Western blots indicated a slight reduction in protein stability, but surface expression was not altered in oocytes.

In summary, we found a Glut1 mutation with relevant functional changes in a family with constant spastic paraplegia and paroxysmal dyskinesia. Constant spastic paraplegia has not previously been described in patients with Glut1 mutations. Therefore, this family enlarges the clinical picture of this syndrome, which suggests that Glut1 mutations may be more common than previously assumed, and that patients with other forms of paroxysmal dyskinesia should be screened for mutations.

The German participation in the 1000 Genomes Project

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The international Human Genome Project has, with participation of German groups, established the reference sequence of the human genome. With the advent of next generation sequencing technologies, it has now become feasible to extend this analysis to a detailed characterisation of the genomes of individual humans, an essential basis for the discovery and understanding of the genetic variants that influence human disease. The analysis of individual genomes will provide the missing link to translate the wealth of recent association findings into an individual understanding of how the phenotypes are generated. In response to this, the 1000 Genomes Project (www.1000genomes.org) has been launched in January 2008 by a number of international centres. In August 2008 the MPIMG joint this initiative. The project is divided in a pilot and a full-project phase. Within the first period three pilot projects were designed. Under the first pilot project, researchers were sequencing 60 HapMap samples from three different populations at low coverage. The second pilot involved sequencing two trios - parents and child - of European and African descent at high coverage. The third pilot project aims to sequence 1,000 genes in 1,000 individuals at high coverage. The MPIMG participated in the first two pilot projects producing over 100 Gigabases of high quality mappable reads. The pilot phase ended with the data freeze from October 24th. At the meeting we will present the results of the analysis of the pilot project.

This project will be key for a further understanding of genetic variation and hence have a significant importance for basic biomedical research and commercial exploitation.

Analysis of innate defence factors in esophageal and gastric cancer

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Some Innate Defence Factors (IDFs) of the first frontline of defence against invading bacteria are discussed as potential tumor suppressors like the defensin peptide DEFB1 and the SRCR protein DMBT1. Other members of the defensin and SRCR protein families like DEFA6 and Mac2bp were suggested as potential biomarkers for colon adenocarcinoma and for the prognosis of stage I non-small cell lung cancer, respectively. Therefore, the detailed investigation of IDFs in esophageal and gastric cancer might lead to interesting new findings. The objective of the present study is to determine the expression-level of mainly defensin genes and of selected SRCR genes in esophageal and gastric tumor samples as well as in the corresponding normal tissues. Obtained expression data will be correlated with clinical parameters. A comparison between the expression-level of IDFs in adenocarcinoma of the esophagogastric junction and distal stomach cancer as well as squamous cell carcinoma of the esophagus might reveal new starting points for diagnosis, prognosis and therapy. Furthermore, our aim is to analyse candidate IDFs in functional cell-based assays like proliferation-, invasion- and migration-assays by creating stably transfected isogenic cell lines. On the NGFN Meeting 2008 we are going to present our preliminary results of the outlined project.

Abbreviations used:

IDFs: Innate Defence Factors; DEFB1: Beta-defensin 1; SRCR: Scavenger Receptor Cysteine-Rich; DMBT1: Deleted in Malignant Brain Tumors 1; DEFA6: Alpha-defensin 6; Mac2bp: Mac-2 binding protein

National Genome Research Network

Poster presentation abstracts

Symposium II

Systems Biology

Identification and quantification of protein-protein interactions in neurodegenerative diseases using mass spectrometry

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Neurodegenerative disorders (NDDs) such as Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis and certain spinocerebellar ataxias share common cellular and molecular mechanisms that drive disease formation. These diseases are characterized by the damage of neuronal cells caused by the aggregation and deposition of insoluble, misprocessed proteins. In order to elucidate the disease networks extensive information of protein-protein interactions (PPIs) is very crucial. We are using SILAC (stable isotope labelling with amino acids in cell culture) - based quantitative proteomics to screen for protein interaction partners of proteins involved in NDDs. In addition, we are investigating how disease associated mutations affect the binding and thereby influence the pathogenesis of neurodegenerative disorders. Bait proteins, representing either wild-type proteins involved in NDDs or proteins with disease associated mutations, are expressed in HEK293F suspension culture cells and immobilized on beads. In order to identify and quantify specific interaction partners of the bait proteins, a pull-down assay with cell lysate from heavy SILAC labeled neuroblastoma cells is performed. In parallel, control pull-downs are carried out with lysates from light SILAC cells and control baits. Proteins binding to both baits are eluted, combined and analyzed by LC-MS/MS. Specific interaction partners are detected by their increased abundance in the heavy form. In contrast, non-specific contaminants are detected with a 1:1 ratio and can thus be excluded effectively. Similarly, the binding characteristics of wild-type and mutant proteins are compared, which will help to understand misfolded protein aggregation and disease progression in NDDs.

Detecting novel connections between neurodegenerative diseases: the NGFN-Plus consortium IG NeuroNet

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Neurodegenerative diseases like Alzheimer's, Parkinson's, or Huntington's disease affect millions of people and are devastating for the patients. The molecular mechanisms of neurodegeneration are still largely unclear, although some lines of evidence suggest that similar molecular programs may be altered in these illnesses. As part of an alliance of nine research groups, we have started to establish an integrated genome research network called IG NeuroNet for the systematic analysis of connections between neurodegenerative diseases. Our aim is to combine functional genomics and proteomics with bioinformatics to predict alterations in the molecular networks of neurodegenerative disease processes. The eight subprojects of NeuroNet are organised as closely interconnected modules. Module 1 is responsible for the systematic generation of protein-protein interaction and phenotype networks. In module 2, the generated networks and predicted disease pathways are systematically perturbed by RNAi and drug molecules to gain insight into the interplay of network structure and function. Module 3 stores, integrates, and processes the results from modules 1 and 2 and exchanges information. The central research perspective of NeuroNet is to construct connectivity maps from the information generated in the subprojects to point out new links between disease proteins, phenotypes, and small molecules.

Large-scale rna interference screens and high-content analysis to dissect cellular pathways

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A limited number of conserved signaling pathways are crucial for normal development and homeostasis. These pathways control many biological functions and their dysregulation has been implicated in many diseases, from developmental defects, to cancer and neurodegeneration. Novel approaches such as high-throughput RNA interference (RNAi) have become an important experimental strategy to assign functions to many uncharacterized genes. Here, we describe massively parallel phenotyping of cells to map the functional space of human cells on a genome-wide scale. We have developed rapid and robust methods for measuring multi-parameter phenotypes. After depletion of transcripts on a genome-wide scale, cells are individually images and classified to map the phenotypic space based on morphological signatures of single cells. Morphological signatures were based on a range of cellular descriptors such cell number, shape and other parameters. These morphological signatures were used to build networks of gene functions. Phenotypes can be accessed through the GenomeRNAi database (http://rnai.dkfz.de). As part of NGFN-plus, we will generalize these experimental and computational approaches to predict interaction networks of genes and small molecules.

Biomarker discovery via stable isotope metabolic labeling of a trait anxiety mouse model

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Anxiety disorders affect ~20% of the general population. To identify protein biomarkers for anxiety disorders, we are comparing the proteomes of mouse models of high (HAB), normal (NAB) and low (LAB) anxiety-related behavior by quantitative mass spectrometry. A sensitive and accurate proteomics platform for biomarker discovery based on metabolic labeling of mice with the stable isotope ^{15}N and comparison with unlabeled ^{14}N mice has been established. Animals were fed with a ^{15}N- enriched diet based on chemolithoautotrophic bacteria. ^{15}N incorporation rates in brain and plasma were then assessed and resulted in up to ~92% labeling in brain tissue. For biomarker discovery, cortex synaptosomes from ^{14}N HAB and ^{15}N NAB mice were compared revealing differentially regulated proteins between the two groups. After Western blot verification, the candidate biomarkers will provide information on pathways relevant for anxiety pathophysiology with the possibility to be translated into clinical diagnostic applications.

IG mutanom - systems biology of genetic diseases

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Cancer, like many other diseases, is caused by disturbances in the complex networks of biological processes in the organisms. Prevention, diagnosis and therapy of these diseases require a detailed understanding of these processes in health and disease. Application of techniques from the area of functional genomics on the individual patient, combined with the development of systems, that are able to model the disease process are now required. The Mutanom project (www.mutanom.org) is an Integrated Genome Research Network (IG) funded through the NGFN Plus Research initiative. The IG Mutanom aims to characterise the functional consequences of somatic mutations and to develop Systems Biology models that predict the outcome of such genetic alterations on a molecular pathway level, cellular and organism level. Initially our effort will concentrate on characterising „driver" mutations i.e. mutations that occur in cancer due to selective pressure promoting cancer progression. A core set of mutations that frequently occurs in breast, prostate and gastrointestinal cancer tissues has been identified and additional mutations will be selected through new generation sequencing approaches. A predictive model will be developed from the quantitative molecular information on signalling pathways obtained from combining functional genomics, proteomics, cellular assays, model organism and clinical data. The developed model and pathway information can then be applied to other genetic diseases and will be systematically exploited to identify new drug targets and improve our understanding on the action and side effects of drugs. Hence, we expect this approach and the combined infrastructure to become a key instrument in improving diagnosis and therapy of cancer and many other complex diseases. The aims and overall structure of the project will be reported here.

Generation and systematic analysis of protein-protein interaction networks for cytoplasmic protein-tyrosine kinases in human cancer

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Protein-tyrosine kinases (PTKs) are important regulators of intracellular signal-transduction pathways and perturbation of signaling by mutations and other genetic alterations results in deregulated kinase activity and malignant transformation. In this project, we aim at the generation of a comprehensive protein interaction network for human cytoplasmic protein-tyrosine kinases and their mutant counterparts that were identified by bioinformatics and sequencing approaches. For this we will use high-throughput yeast two-hybrid (Y2H), yeast three-hybrid (Y3H) and MYTH-based protein-protein interaction (PPI) screens, mass spectrometry-based proteomics and bioinformatics. For the PPI screen a prey-library with more than 20,000 genes is available in our lab. It contains ~16,000 unique, full-length cDNAs and covers approximately 75% of the human genome. Standardized methods for data validation with pull-down assays, co-immunoprecipitations and co-localization studies are established. The TAP-MS protein complex information will then be utilized for the systematic identification of modulators of Ras-Raf-ERK, JNK-STAT and PI(3)K signaling using cell-based reporter assays. This includes systematic RNAi knock-down as well as overexpression experiments with established cell model systems in order to identify proteins that influence signaling in human malignancies. The outcome of this project can be utilized for the identification of new tumor suppressors or oncogenes in patient genotyping and phenotypic analyses. Furthermore, this project may contribute to the elucidation of new pathways in oncogenic kinase signaling and the identification of new drug targets for therapy development.

Systematic gene expression profiling of a series of mouse models reveals co-expressed genes

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Aims: One of the largest expression profiling data sets from diverse mouse mutant lines (MMLs) submitted to the German Mouse Clinic (GMC) was analysed adressing the following questions: 1) How efficient is our strategy of organ selection with regard to the detection of regulated genes?

2) Can we identify groups of co-expressed genes?

3) Is there functional overlap between regulated genes?

Methods: We assessed transcript profiles of organs using a genome-wide cDNA microarray. Organs for gene expression profiling were selected based either on conspicuous phenotypes in other GMC phenotype screens or on previous knowledge of gene function. For the identification of significantly regulated genes SAM was used. Functional classification of genes analysed based on Gene Ontology (GO) annotations.

Results: In total, 90 organs of 46 different MMLs were analysed for gene expression patterns. Changes at gene expression levels were identified in 45 of 90 analysed organs. We identified genes that were repeatedly co-expressed in the same organ of independent MMLs. The analysis of GO annotations did not reveal evidence for functional relation between co-expressed genes.

Conclusions: With regard to the questions that we addressed with our mouse expression profiling dataset we find that:

1)The knowledge-biased molecular phenotyping screen is at least as efficient as other GMC screens in terms of detecting novel phenotypes.

2) We identify groups of genes that are co-expressed in different MMLs. The set of expression profiles that we have generated thus provides a reference library that we may use to relate profiles of new MMLs in the GMC.

3) So far, we find no GO based functional overlap within groups of co-expressed genes. Some overlap in GO functional annotations was evident among the entire dataset of regulated genes. Analysis of gene promoters for evaluation of relationships between the identified co-expression groups is currently performed.

Protein microarrays as tool for cancer systems biology

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Protein microarrays are a sensitive tool to yield quantitative data on changes of the phosphoproteome with high sensitivity and excellent sample capacity. Technically, two different routes can be taken to monitor protein abundance and the turnover of protein phosphorylation in the microarray format. First, a specific target protein can be detected by employing a multiplexed microspot immunoassay. This approach requires two different antibodies recognizing spatially different epitopes, and has been realized for the quantitative description of Erk1/2, STAT and AKT-1 signaling. A software program "Quantpro" was developed for the statistic analysis of signals and the presentation of time-resolved quantitative data[1]. Second, samples can also be printed directly on the microarray. In this case, the detection of a specific protein, or a certain phosphorylation-site, is performed with a single, but highly specific antibody per slide. This approach, also known as reverse phase array (RPPA), permits protein profiling from as little as only 20,000 cells with a sensitivity in the fg-range[2]. The capacity is limited to the analysis of up to 800-1000 different samples per microarray. Routine applications involve analyzing the activation status of signaling pathways[4], for example after RNAi-based silencing experiments[3], as well as protein profiling of tumor biopsy samples using a set of >80 RPPA validated antibodies. Results from the analysis of colon tumors and gastrointestinal tumors will be shown[5].

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Modeling ERBB receptor-regulated G1/S transition to find novel targets for de novo trastuzumab resistance

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Trastuzumab is a monoclonal antibody targeting overexpressed ERBB2; however, de novo resistance is still a serious issue, requiring additional targets. Therefore, we focused on a network combining ERBB signalling to G1/S transition of cell cycle to determine the potential perturbation points in resistant cell system. We constructed a literature-based network of 18 proteins, with three ERBB receptors, key signalling proteins, key transcription factors and cell cycle regulators. We employed Boolean logic to model regulatory interactions and simulated loss-of-function of proteins. Simulation results were tested experimentally by producing single knockdowns of all network proteins, and double knockdowns of ERBB receptors. As output, we examined effects of knockdowns on the phosphorylation of retinoblastoma protein, the marker of G1/S transition. Out of 18 network proteins, Cyclin D1, Cyclin E1, CDK4, ER alpha and C-MYC were identified as potential candidates to be targeted. Combinatorial targeting of ERBB receptors or key signalling intermediates, previously thought to be promising candidates, were not determined as potential targets in both RNAi and chemical inhibitor-based experimental setups in de novo resistant cell system compared to trastuzumab sensitive cells. Finally, using quantitative protein array data, we reverse-engineered known and novel interactions in the network.

Quantitative proteomics of growth factor receptor and hormone receptor signalling

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One of the most common female malignancies is breast cancer. Breast tumors are distinguished by the expression of the estrogen receptor (ER), or by the expression of ERBB2, an orphan receptor of the epidermal growth factor receptor family. More than 60% of human breast tumors are ER-alpha positive, and thus anticipated that patients can benefit from anti-estrogen therapies. ERBB2 is over-expressed in 25-30% of human breast tumors and targeted therapies aiming at its inhibition are already clinically approved. However, in the clinic only 1/3 of the patients benefit from a targeted therapy and molecular factors to predict therapy response still need to be identified. Thus, quantitative protein microarray-based proteomics are employed to unravel the interplay between growth factor and hormone dependent signaling including their downstream signaling.

Technically, two different protein microarray-based methods were explored for quantitative proteomics. First, the microspot immunoassay (MIA) is useful to monitor rapid signaling events directly downstream of the receptors with high accuracy (Korf *et al.*, Proteomics 2008). Second, the reverse phase protein arrays (RPPA) are a useful tool for semi-quantitative protein profiling to evaluate the changes of abundance and activation status of hundreds of samples and up to hundred target proteins in parallel (Löbke *et al.*, Proteomics 2007, Haller *et al.*, J. Pathol. 2008). By employing a combination of both methods, hormone and growth factor receptor signaling are currently elucidated in human breast cancer cell lines (HCC1954, BT-474, SK-BR-3) regarding cell cycle progression, apoptosis and migration as tumor-relevant key steps.

Immuno-phenotyping at the German Mouse Clinic. The clustering of T cell subsets.

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The phenotyping platform of the Immunology Screen at the German Mouse Clinic uses multi-color flow cytometry to identify immunodeficiencies in mutant mouse lines. Two staining panels enable us to identify major leukocyte lineages and T cell subsets. T cell subsets are discriminated regarding the expression of homing and activation markers CD44, Ly6C and CD62L. On our poster we present the analysis of T cell subsets in individual wildtype mice, arraying CD4 and CD8 Tcell subset with similar patterns into clusters. The analysis revealed a strong interaction of CD4 and CD8 T cell subsets. Moreover, we show that whole-group averaging of the proportions of Tcell subsets may not appropriately characterize the situation of Tcell subsets in wildtype mice. The presented type of analysis will help specifying subtle immune phenotypes in mutant mouse lines.

Analysis of genetic factors in disease susceptibility: An integrative systems biology concept

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The hypothesis of complex associations between genes harboring structural mutations, as well as polymorphisms in regulatory regions, is a major challenge that can be tackled by a combined analysis of expression data, metabolic pathways and protein interaction networks. Such a systems biology approach also includes the objective to identify genes from QTL regions as susceptibility factors (Hutz 2008). For both tasks, identification of disease-related genes and modeling of their combined effect, respectively, we are currently developing a bioinformatics platform, which will (1) integrate data of different biological systems in a relational database design (incorporating Gene Ontology, KEGG, BIND, HPRD data). The database scheme provides consistency and integrity as well as quick access through index-optimized table structures, which is mandatory for interactive whole genome analysis; (2) provide statistical algorithms for identification of dysregulated pathways in candidate gene lists from QTL and microarray data; (3) be capable of testing for above-average proximity on the sequence level of candidate genes for each pathway / network. This will be realized using permutation tests on a proximity measure based on the minimum spanning tree of gene loci and a clustering validation index (Davis-Bouldin). We assume the disease-related genes from certain pathways or interacting proteins to be associated with the haplotype structure on the sequence level, especially with respect to co-adaptation of interacting proteins or regulatory benefits from aggregation in gene clusters. Estimation of epistatic effects between candidate genes will eventually be derived from a combined representation of network data (gene ontology, pathway and protein interaction data). Due to the explorative character of the overlaid network data, a graphical display for manual review is planned, with automatized statistical analysis features being subject to extension in future versions.

SBML2LaTeX: Conversion of SBML files into human-readable reports

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The XML-based Systems Biology Markup Language (SBML) has become the standard format for storing models of biochemical systems. SBML allows for defining complex models of molecular interactions and cellular processes. It is not necessary to type XML manually; over one hundred software tools now support SBML, including many with intuitive graphical interfaces. Many tools also support visualizing and saving molecular interaction graphs, but important details such as kinetic rate equations, user-defined functions, events, model notes, and annotations given in the Systems Biology Ontology (SBO) are usually not made explicit in the graphical presentations. To detect potential errors or to gain an overview of the model as a whole, it is necessary to examine the full content of the SBML file, but the unfriendliness of XML to human readers makes this an inconvenient and difficult task. We therefore present SBML2LaTeX, an on-line converter for SBML files. SBML2LaTeX produces human-readable files in various formats, including PDF, DVI, PS and TeX. Several settings allow for customization of the output, such as for instance the paper size, orientation (portrait or landscape), font sizes and font styles. SBML2LaTeX covers all constructs defined in the latest level and version of SBML and is able to typeset complex kinetic formulas. It computes the derived units for all SBML elements and shows warnings if kinetic equations cannot be evaluated to the correct units. All information is presented in clearly arranged tables, reaction equations and plain text, simplifying the task of understanding and communicating the model as well as detecting and correcting errors. SBML2LaTeX can be accessed at

http://webservices.cs.uni-tuebingen.de/webservices/sbmlconverterGridJob/create.

Modeling metabolic networks: a comparison of rate laws in combination with various parameter optimization strategies

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To understand the dynamical behavior of cellular systems over time, mathematical modeling is often necessary and comprises three steps:

(1) measurement of participating molecules in wet-lab experiments,

(2) assignment of rate laws to each reaction, and

(3) determination of the parameters for each rate law so that the model behavior is in agreement with the measurements.

This overall process with its numerous choices and the mutual influence between them makes it hard to single out the best modeling and parameter estimation approach for a given problem. We investigate the modeling process using multiple kinetic equations together with various parameter optimization methods for the well-characterized valine and leucine biosynthesis in *C. glutamicum*. We derive seven dynamic models based on generalized mass action, Michaelis-Menten and convenience kinetics as well as the stochastical Langevin equation. The parameters of each model are estimated using eight optimization strategies. To determine the most promising modeling approaches together with the best optimization algorithms we accomplish a two-step benchmark:

(1) coarse-grained comparison of the algorithms on all models and

(2) fine-grained tuning of the best optimization algorithms and models.

To analyze the space of the best parameters found for each model, we apply clustering, variance and correlation analysis. A mixture model based on the convenience rate law and the Michaelis-Menten equation, in which all reactions are assumed to be reversible, is the most suitable deterministic modeling approach followed by a reversible generalized mass action kinetics model. A Langevin model is advisable to take stochastic effects into account. To estimate the model parameters three algorithms are particularly useful. For first optimization attempts the settings-free tribes algorithm yields valuable results. Particle swarm optimization and differential evolution provide significantly better results with appropriate settings.

SBMLsqueezer: a CellDesigner plug-in to generate kinetic rate equations for biochemical networks

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The development of complex biochemical models has been facilitated through the standardization of machine-readable representations like SBML (Systems Biology Markup Language). This effort is accompanied by the ongoing development of the human-readable diagrammatic representation SBGN (Systems Biology Graphical Notation). The graphical SBML editor CellDesigner allows direct translation of SBGN into SBML. For the assignment of kinetic rate laws, however, this process is not straightforward, as it often requires manual assembly and specific knowledge of kinetic equations. SBMLsqueezer facilitates exactly this modeling step via automated equation generation, overcoming the highly error-prone and cumbersome process of manually assigning kinetic equations. For each reaction the kinetic equation is derived from the stoichiometry, the participating species as well as regulatory relations. The types of kinetics considered are numerous, e. g., generalized mass-action, Hill, convenience and several Michaelis-Menten-based kinetics, each including activation and inhibition. SBMLsqueezer covers metabolic, gene regulatory, signal transduction and mixed networks. Whenever multiple kinetics are applicable to one reaction, parameter settings allow for user-defined specifications. The resulting model can be simulated in CellDesigner or with external ODE solvers. Furthermore, the equations can be exported to SBML, LaTeX or plain text format. SBMLsqueezer considers the annotation of all participating reactants, products and regulators when generating rate laws for reactions. Thus, for each reaction, only applicable kinetic formulas are considered. This modeling scheme creates kinetics in accordance with the diagrammatic representation. In contrast most previously published tools have relied on the stoichiometry and generic modulators of a reaction, thus ignoring and potentially conflicting with the information expressed through the process diagram. SBMLsqueezer is freely available.

Human TOPONOME project: Progress report

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Based on our earlier publication of the Toponome technologies (Schubert, W. et al. *Nat. Biotechnol.* 2006, 24, 1270 - 1278; Nat. Protoc. 2007, 2, 2285-2294) for the functional mapping of protein networks in the one cell or tissue section (research highlight, *Nature* 2006, 443, 609), we have recently established 4 toponome facilities (centers) at different universities in Germany and England. These centers have started to actively work in different fields addressing the neurotoponome, the cancer/sarcoma toponome and the chronic inflammation toponome. Their final goal is the complete functional annotation of the human toponome in health and disease (structure-bound protein network code directly in cells and tissues). Major results of the last year were: We found a protein custer motif controlled by two lead proteins in prostate cancer; identified the apoptosis toponome in hepatocyte nuclei; found new regions in the murine hippocampus by mapping the synaptic toponome; found two fundamental rules governing the toponome in tumor cells: the dissimilarity rule and the geometry rule: the cell combines only those proteins as interlocked clusters on the cell surface, which are structurally highly dissimilar. Each cluster occupies a space with unique geometric features as part of the complete protein network code of the cell. Industry partners provide large protein binding tag libraries, and a toponome data base is presently established: it contains higher level rules of protein network organization and function, from protein abundance through protein clusters and cluster networks in the same biological morphologically intact structure. The publication of a three symbol code for the organized proteome (the toponome) (Schubert, W. *Cytometry A* 2007, 71, 352-360) has received the ISAC best paper award 2007 (awarded in 2008). A specific application of toponomics in the field of neuroblastoma research is presently being established as part of the NGFNplus consortium ENGINE.

iCHIP- sustainable data pool services for Neuroblastoma

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Our integration center iCHIP serves as the central data backbone and mining platform for the Neuroblastoma (NB) consortia. iCHIP is addressing the continuous need for permanent data storage and provision of new data types. Besides 2-dimensional experimental data RNAi-images and clinical specifications are integrated within one platform. Using data from different sources and technologies in a combined analysis is a challenging task. Partially the labs are jointly working on samples of identical patients with different technical assays. Validated patient-dependent information is obtained from the National Central Tumorbank for embryonal tumors, a highly reliable source of biospecimens. We assign the highest possible relevance to standardization of data annotation and analysis as a prerequisite for subsequent valid and reproducible interpretation of research results. iCHIP is ideally suited for supporting meta-analyses demands in medical and systems biology projects to increase the statistical power of conclusions: a unique feature of iCHIP as a research database is that all pooled diverse clinical, histological, phenotypical and experimental data are available for exploitation by means of integrative research. The comprehensive NB-specific parameter set defined in NGFN2 allows the utilization of the wealth of clinical data. The classification of disease-relevant clinical parameters and genetic profiles will improve prognosis and therapy. An enhanced version of the annotation system PIMS from the department of Molecular Genetics at the DKFZ will constitute our automated gene annotation pipeline. Gene-wise and genome-wide comparison views across the various data types will interrelate this species annotation and experimental molecules. Model hypotheses, e.g., the effectiveness of proposed therapies and the quality of putative targets for therapy development can be evaluated based on already existing detailed clinical information and experimental time course data.

Ranking the biomedical literature for optimised experimental designs

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The analysis of biological databases and large datasets from high-throughput molecular experiments can benefit from the integration of biomedical literature information. For instance, text mining methods can be used to design an experiment with selected features. Most of the biological database entries are linked to scientific abstracts through the Medline database which contains millions of citations. Few available text mining tools allow to rank many abstracts within practical time according to their relevance to a particular topic. The flexibility of such tools is mandatory to handle any biomedical topic, even if the topic is not well annotated in existing databases.
We have implemented a statistical method which scores the Medline records by using noun frequencies in a selection of abstracts relatively to the whole Medline. It allows the scoring of one million abstracts in 70 seconds. The selection of abstracts can also be compared to a particular background set to take into account over-representation of some topic. We have applied the method to protein-protein interaction (PPI) data to automatically retrieve phosphorylation-dependent interactions among 17 000 records. This topic is not directly annotated in the Medline manual curation process, and an expert query in Pubmed returns few abstracts. While the separation of phosphorylation-dependent interaction abstracts from the rest of Medline is very accurate (accuracy=99%), their separation from other PPI abstracts is less accurate (accuracy=81%) when evaluated by a leave-one-out cross validation with random abstracts. Yet, the manual validation of the best results shows many true positives. The method was efficiently applied to PPI data and can be used for any topic. It allows to save time when used in the analysis of the results from a high-throughput experiment. A web server is available with a simple and powerful interface at: http://cbdm.mdc-berlin.de/tools/medlineranker.

National Genome Research Network

Poster presentation abstracts

Symposium III

Genome Regulation

Modulating the action of nuclear receptors by natural products

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Natural products have a long history of success as biologically active leads for drug development. Furthermore, they have a high potential for the development of nutraceuticals that can be used for the prevention of metabolic diseases. Medical treatments for type 2 diabetes often include synthetic activators of nuclear receptors such as PPARgamma to sensitize the body to insulin. However, while improving insulin signalling, synthetic drugs such as the thiazolidinediones implicate weight gain due to excessively activated adipogenesis. To uncouple insulin sensitization from triglyceride storage by modulating PPARgamma activity might be the most effective strategy for treating metabolic disorders such as insulin resistance. Selective nuclear receptor modulation is a novel pharmacological approach that can be studied efficiently by genomic approaches. We show herein the discovery and systematic characterisation of natural products with novel strutures that can be used for specifically activating PPARgamma. These compounds have a high potential for application in drug development and the production of nutraceuticals.

Transcriptional key mechanisms in epilepsy: Induction of T-type calcium channel $Ca_V3.2$ expression by zinc

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Brain neurons contain substantial amounts of Zn^{2+}, which plays multiple roles in cellular functions. Whereas the release of Zn^{2+} into the interstitium reportedly modulates various neurotransmitter receptors and ion channels, only little is known about the effects of intracellular Zn^{2+} (Zn^{2+}_{in}) on transcription of genes critical for neuronal excitability after brain insults such as status epilepticus. Here, we address whether Zn^{2+} controls the transcription of Ni^{2+}-sensitive Ca^{2+} channels, i.e. R/T-type Ca^{2+} currents mediated by the a_1 subunits $Ca_V2.3$ and $Ca_V3.1$-3.3. In NG108-15 neuroblastoma cells, transient exposure to 200 µM Zn^{2+} under depolarizing conditions (50 mM KCl) led to Zn^{2+} influx via L-type (BayK-sensitive) Ca^{2+} channels, and to increased mRNA transcription of $Ca_V3.2$, but not of other R/T-type Ca^{2+} channels. Bioinformatic analysis of the $Ca_V3.2$ promoter revealed a 1.164bp fragment within the 5´ UTR-flanking genomic sequence that encompasses several evolutionary conserved transcription factor binding sites. Exposure of NG108-15 cells to Zn^{2+} strongly induced transcription of a luciferase reporter plasmid under control of the 1.164bp $Ca_V3.2$ promoter fragment. Similar effects were induced by the NO-donor Na^+ nitroprusside, which causes liberation of intracellular Zn^{2+} bound to endogenous chelators. Overexpression of MTF-1 activated the $Ca_V3.2$ promoter to similar levels as exposure to Zn^{2+}. We are currently analyzing the human $Ca_V3.2$ promoter for SNPs to sensitize humans for epileptic excitotoxicity. Our findings implicate $Ca_V3.2$ as a novel target for transcriptional upregulation via transient increases in intracellular free Zn^{2+}. Since brain injuries are accompanied by marked elevations in intracellular free Zn^{2+}, and $Ca_V3.2$ upregulation profoundly enhances neuronal discharge, upregulation of $Ca_V3.2$ transcription by zinc represents a novel mechanism to antagonize epileptogenesis.

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Conservation of transcriptional autoregulatory feedback loop in vertebrates

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An *autoregulatory feedback loop* is an elementary motif observed in transcriptional regulatory networks. The cells utilize direct autoregulation in many fundamental processes, for example to guarantee fast transcriptional responses or to provide multiple stable states of gene expression. Therefore, the conservation of autoregulatory feedback loops in the course of evolution is of prime interest. We study the enrichment of the number of autoregulatory feedback loops among higher organisms. First, the number of loops constructed out of predicted transcription factor binding sites is counted. Next, we compare the result to an estimate obtained by assuming that each (conserved) gene has the same chance to be a target of a given transcription factor or by assuming that each conserved promoter position has an equal chance to become a binding site of the transcription factor. Our analysis shows that the numbers of putative autoregulatory feedback loops conserved between human and fugu, danio or chicken are significantly higher than the estimations. Additionally, we demonstrate that the conserved autoregulatory binding sites tend to concentrate around genomic locations corresponding to the transcription start sites of the respective transcription factors. We conclude that transcriptional autoregulatory feedback loops constitute a core transcriptional network motif and their conservation has been maintained in evolution of higher vertebrate organisms.

Quantitative models and prediction of regulatory interactions

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Recent experimental advances set the stage to investigate gene regulatory mechanism at an unprecedented resolution. In previous work we have shown how large-scale binding data can be utilized to model transcription factor DNA interactions in a more quantitative fashion. Here we present different applications of our model.

As a first application we have developed a method called PASTAA which quantifies the association of a transcription factor with a coherently expressed group of genes, for example a tissue category. PASTAA assumes that a list of genes can be ranked (1) according to their membership in a specified group and (2) according to the regulatory potential of a transcription factor, as quantified by our model. We validated our method by showing that it successfully explains ChIP-chip data in yeast and vertebrates. When applied to large-scale expression data, PASTAA robustly recovers many known associations and factors which are specifically expressed in a given tissue. As a second application, we suggest a method to rank comprehensive lists of transcription factors according to their binding affinity and changes in binding affinity. The latter might be induced by sequence variations, such as regulatory SNPs. We present a statistical analysis and a normalization approach which allows to directly compare the different affinities from different factors and their induced changes.

Pseudogenes as a source of trans-NAT seeds

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Pseudogenes are the result of gene duplication (genomic DNA duplication, retrotransposition) or defective genes. Sometimes they look so much like real genes that they confuse gene prediction algorithms. Some comparative studies use them as a reference: loss of human vitamin C synthesis, loss of hemoglobin in Antarctic ice fishes, etc. It is commonly believed that pseudogenes are junk DNA because of their lack of functionality. However, while no coding ability has been ever detected, some publications showed evidence of non-coding regulation. At first, the relevance of these studies were not appreciated by the scientific community and had to be re-discovered after the publication of a popular paper in 2003. This study was refuted three years later but eventually encouraged later works. Recent studies in different organisms again point out a certain degree of non-coding regulatory function. A final conclusion regarding the role of non-coding DNA which summarizes all of these efforts can not easily be made because of the small amount of evidence and because different genomes were used in the studies, therefore the comparison between them is more difficult.

In this work we present a novel approach. The work´s hypothesis is that the pseudogenes after some evolution could be a source of trans-antisense that regulates their respective parental genes. A genome wide analysis based on the whole set of EST entries contained in GenBank for a given organism is used to probe it. At the moment the analysis is being done only on the Human genome but in the future it could easily applied to different genomes.

A genome-wide RNAi screen to identify modulators of human P38 signalling

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The P38 signal transduction pathway has impact on numerous biological processes via stress activation, including on processes such as cell cycle control, cell death, inflammation, and cancer. Within Ig-CSG, we apply the RNA interference (RNAi) technology, using small interfering RNA (siRNA) for systematic high-throughput functional genomic screening. We screened for genes influencing P38 MAP kinase signalling when knocked-down using a human genome-wide siRNA library that contains over 21.000 siRNA pools. Therefore, a p38-specific luciferase reporter cell line was transfected in 96-well format and assayed for reporter gene expression reflecting the activation status of P38 signalling. Data was processed in a high-throughput analysis pipeline comprising multiple pre-processing, normalization and quality assessment steps. Thus, we acquired scored values of activation or inhibition in an unbiased and objective manner, and were able to audit critical steps of the analysis procedure. Primary hits were validated by secondary screening using phospho-specific antibodies in flow cytometry, measuring the changes of the P38 activation level in dependence on the interference of the genes. By these means, we could identify a number of genes/proteins with a modulating effect on the P38 signalling pathway. These genes were then further analyzed for their role in biological processed that are connected with p38-signaling, such as cell cycle, proliferation and apoptosis. Moreover, we were analyzing for their direct interaction with members of the P38 signaling-pathway.

Identification of targets for KSHV-encoded miRNAs

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MicroRNAs (miRNAs) are noncoding small RNAs that play important roles in a variety of biological pathways by interacting with the 3'UTRs of target genes. This interaction leads to downregulation or impaired translation of certain transcripts, and recent studies have linked the expression of miRNAs to carcinogenesis and viral pathogenesis. Herpesviruses constitute a family of human pathogens that contribute to a variety of different diseases including tumors and lymphoproliferative disorders. The Kaposi's sarcoma associated herpesvirus (KSHV) encodes 12 miRNAs, but only a few cellular targets have been identified until now and nothing is known about their biological function during the infectious cycle. To identify cellular targets of KSHV-encoded miRNAs we used a lentiviral system for stable expression of miRNAs in either B-cells or endothelial cells and performed microarray analyses. A multitude of cellular genes responded upon expression of KSHV-encoded miRNAs, and a detailled bioinformatic analysis of KEGG signalling pathways revealed that distinct pathways are targeted in different cell types. Candidate genes, responding reproducibly to the viral miRNA expression and carrying miRNA-complementary sites within their 3'UTRs were validated by a luciferase- and 2'O methylated oligonucleotides-based reporter system, as well as Western Blot analyses and functional assays.

NPM-ALK kinase activity influences miRNA expression in ALK+ Anaplastic Large Cell Lymphoma (ALCL)

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Malignant lymphoma is a relatively frequent disorder and the third most common cancer of childhood. There are more than 30 subtypes of malignant lymphoma, including Hodgkin's lymphoma (HL), and B- and T-cell non-Hodgkin lymphomas (NHL). ALK+ ALCL represents a distinct type of NHL mainly of T- cell phenotype. This entity is characterized by the t(2;5) chromosomal translocation, resulting in the expression of a chimeric protein called NPM-ALK. We recently reported that STAT3 and C/EBP transcriptional factors are constitutively activated in ALK+ ALCL and that its expression is dependent on NPM-ALK kinase activity. These transcription factors are well-characterized, however, the mechanisms of posttranscriptional regulation are only partially understood. Therefore, the characterisations of microRNAs (that regulate gene expression on the posttranscriptional level) appear to be very important for further studies. In the context of further biological characterisation of ALCL we determined expression pattern of the 365 specific miRNAs in ALK+ALCL cell lines in comparison to T-lymphocytes. Accordingly, 17 miRNAs were differentially expressed and five of miR-17-92 cluster showed a significant difference to T-lymphocytes. Suspension cells originating from T-lymphocytes like ALCLs show very low transfection efficiency by standard supplied methods. Efficient transduction of ALCL cells by lentivirus containing the GFP reporter was achieved, and will be demonstrated by FACS analysis. In summary, The NPM-ALK downregulation and downregulation of NPM-ALK downstream targets (STAT3 and C/EBP) by specific shRNAs in ALCL cells showed influence on miRNA (miR-17-92) cluster expression. This data suggest that miRNA-17-92 cluster has important function in ALK+ ALCL biology characterization and future consideration as therapeutic target.

The role of hypoxia-induced N-myc down-regulated gene 1 (NDRG1) in glioma biology

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N-myc down-regulated gene 1 (NDRG1/Cap43) is an intracellular protein that is induced under a wide variety of stress and cell growth-regulatory conditions. In a comparative proteomics analysis screening for hypoxiaassociated candidate genes using 2D gel electrophoresis and mass spectrometry, we identified and validated NDRG1 as being robustly up-regulated with sublethal hypoxia in various human malignant glioma cell lines. At an oxygen level of 1%, we also observed NDRG1 to be induced in untransformed astrocytic cells, but to a lesser extent. Interestingly, in primary glioma-initiating cells that had been cultured in non-differentiationinducing conditions, expression of NDRG1 was detectable at low constitutive expression levels in normoxia, but not inducible by hypoxic treatment. As examined in knock-down glioma transfectants, we found the hypoxia-mediated induction of NDRG1 to be dependent on hypoxia-inducible factor (HIF)-1alpha, but independent of p53 signaling. Further, immunohistochemistry of human glioma °II to °IV specimens demonstrated a strong correlation between NDRG1 expression and malignant glioma transformation. In glioblastoma specimens, expression of NDRG1 was markedly increased in close proximity to necrotic tumor areas whereas in grade II and III gliomas expression turned out to be confined to single cells. We cloned the human *NDRG1* gene from glioma-derived cDNA and generated both NDRG1 over-expressing and stable shRNA-mediated glioma knock-down transfectants. Using these cellular tools in several functional *in vitro* paradigms, we currently aim to elucidate the role of hypoxia-regulated NDRG1 and decipher whether its induction influences the responsiveness towards antineoplastic treatment modalities in malignant gliomas. Further work will comprise microarray and proteomics-based approaches to understand more about NDRG1-dependent signaling as well as *in vivo* experiments using orthotopic xenograft mouse models.

Identification of disease-related copy number variation (CNV) in patients with mental retardation by high-dense SNP genotyping microarrays

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We investigated 109 children referred for unexplained mental retardation using Hap550 oligonucleotides arrays (Illumina). Conventional karyotyping did not reveal any abnormality. Data analysis were performed with median normalization and genotypes-specific dosage calculation using R-scripts. We used standard deviation (mean SD: 0.15) and mean absolute deviation (mean MAD: 0.11) of the log2 intensity ratios to assess data quality. We also calculated a signal-to-noise ratio (mean SNR: 5.44) in male DNA samples (median log2 intensity ratio of the X-chromosomal SNPs minus median log2 ratio of the autosomal SNPs divided by MAD). 289 out of the 1.014 identified CNVs were evaluated with 628 quantitative PCRs (2 or 3 each). 55,4% were determined to be true-positive findings. Our experiments are likely to underestimate the true positive rate because we excluded all known CNV polymorphisms. Under the assumption that all detected known CNV polymorphisms are true positive, this rate would be 87,3%. 78,3% of the false positive CNVs were detected in regions defined by < 9 SNPs, 20,2% in 9-20 SNPs and 1.5% in >20 SNPs. Preliminary results revealed 16 *de novo* CNVs, 14 deletions and 2 duplications (14,7%), which varied in size from 125 kb to 13,3 Mb. Seven CNVs were known genomic disorders., whereas four CNVs overlapped with a DECIPHER entry. The remaining 5 CNVs were not described before.

In addition to the *de novo* cases of MR, also patients suffering from an autosomal recesive form of MR were screened in our cohort. We identified two patients with a partial deletion of the *COH1* gene which is mutated in Cohen syndrome. Direct sequencing revealed a stop mutation and a 1-bp deletion, respectively, on the remaining allele.

National Genome Research Network

Poster presentation abstracts

Symposium IV

Animal, Cellular & Tissue Models

Aca12 and *Aca23* - two novel mouse models for microphakia and corneal dystrophies

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Purpose: Aim of the study was the characterization of two novel eye size mutant lines, *Aca12* and *Aca23*.

Methods: The mouse mutant lines *Aca12* and *Aca23* arose from a dominant ENU-screening program using the optical low coherence interferometry (OLCI) technique. Both eye-size mutants were mapped by a genome-wide SNP linkage analysis. For a fine mapping, recombination frequencies between microsatellite markers were analysed.

Results: Up to date 1600 offspring from ENU-treated C57BL/6J mice have been analyzed in an ongoing dominant screening program. 75 of them were identified as putative eye size variants (*Aca1-Aca75*). Confirmation crosses established the variants *Aca12* and *Aca23* as stable mutant lines. *Aca12* is characterized by 7% reduced lens sizes. The *Aca12* mutation was linked to chromosome 14. Sequence analysis of positional candidate genes revealed a transition within the coding region of the gene encoding the fibroblast growth factor *Fgf9*. In the mutant line *Aca23*, anterior chambers were identified to be 34% enlarged. Linkage analysis revealed that the *Aca23* mutation is located on the distal part of chromosome 4. A transition was found in the coding region of the positional candidate gene *Col8a2*, which is expressed in the Descemet's membrane of the cornea. As a further consequence, a thinning and keratoglobus-like protrusion of the cornea was identified in *Aca23*.

Conclusion: The eye size mutants *Aca12* and *Aca23* were established in an ongoing ENU-screening program. *Aca12* and *Aca23* represent novel models for microphakia and corneal dystrophies, respectively.

"Sighted C3H" mice in the vision screen module of the GMC: Identification of a novel mutation site

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Purpose: In the vision screen module of the GMC, "sighted C3H" mice were compared to wild-type C3H/HeH mice, which suffer from retinal degeneration caused by the strain specific *Pde6b*(rd1) mutation.

Methods: All mice were screened for morphological and visual alterations by funduscopy, slit lamp biomicroscopy, laser interference biometry, ERG, and optokinetic drum. Genome wide mapping was undertaken with a SNP linkage analysis. For a fine mapping, recombination frequencies between microsatellite markers were analysed.

Results: In "sighted C3H" mice the mutated *Pde6b*(rd1) allele of C3H/HeH was replaced by the wild-type *Pde6b* allele of BALB/c. Primary slit lamp analysis, funduscopy, and laser interference biometry of "sighted C3H" eyes documented a clear anterior segment, homogenous fundus, and axial length comparable to the wild-type situation. Corresponding results were observed in the secondary optokinetic vision test, since each "sighted C3H" animal scored in at least one of six trials. However, scotopic ERG unexpectedly revealed a lack of the b-wave response. This can be explained only by a new mutation outside of the *Pde6b* locus. Consequently, a genome wide linkage analysis located a putative mutation site on the distal part of chromosome 11. Up to date, fine mapping studies indicated the microsatellites *D11Mit179* and *D11Mit199* as flanking markers of a 12.05 Mbp spanning candidate gene region. Since this interval contains nearly 450 loci, a further fine mapping is in process.

Conclusion: "Sighted C3H" mice, which carry a functional *Pde6b* gene, are still characterized by an abnormal vision due to an altered ERG. Linkage studies point to an additional, not yet identified mutation on chromosome 11 as the causative event.

metaP: Introducing metabolomic platform at the Helmholtz Zentrum München

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Metabolomics is a very fast expanding research field for phenotyping of biological samples with an unbiased approach of characterisation. Especially, either not much pronounced (silent) phenotypes or subsidiary phenotypes could be determined if many different parameters are correlated. At present, two main approaches in metabolomics are performed: targeted (quantification of a chosen set of metabolites) and non targeted (profiling or search for biomarkers).

The Metabolomic Platform (metaP) of the Helmholtz Zentrum München (http://www.helmholtz-muenchen.de/gac-metabolomics/) is designed to mediate progress in science through development of new metabolomic methods and provision of measurement services applicable to man, animal models, plants, environmental samples and ex vivo systems. Part of our activities is related to targeted metabolomics. The quantification is based on the Biocrates Kit Absolute IDQ and covers more than 150 endogenous metabolites like lipids, amino acids, acylcarnitines, carbohydrates and many more. For this, a sample amount of e.g. only 10 µl plasma is needed. The measurements perform very well with high reproducibility. We successfully performed studies in the human kohort KORA and in animal models in elucidating metabolomic effects in complex diseases or drug development, respectively. To facilitate high quality standards and sample tracking we build up a tailor made LIMS.

The processivity of the Metabolomic Platform is reached by integration of different expertise at the campus of the Helmholtz Zentrum München. At present, in the metaP cooperate the following groups: robotics for sample preparation and analyte quantification (LC-MS/MS 4000 QTrap; Jerzy Adamski), high resolution analysis and profiling (FTICR-MS; Philippe Schmitt-Kopplin), biobanking (Thomas Illig) and bioinformatics/project integration (Karsten Suhre).

Steroid metabolism screen

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Steroids control the differentiation and proliferation of cells and tissues. They further participate in the regulation of apoptosis, bone remodelling and neuroregeneration. Severe diseases are caused by monogenic mutations with loss of function of steroid pathway proteins. Defects in steroid metabolism contribute as well to the pathogenesis of many different multifactorial diseases like cancer, diseases of cartilage and bone or neurological diseases. The main focus of the steroid screen is the identification of new animal models for human steroid-related diseases therewith supporting the development of their future therapies. In the primary screening we look for alternations in plasma concentrations of the key steroids testosterone and dehydroepiandrosterone (DHEA). In the secondary screening we offer an option for the measurement of additional steroids, including estradiol, estrone, androstenedione, aldosterone, DHEA-S, DHT, estriol, pregnenolone, progesterone and 17-OH-progesterone. Optional assays for profiling with 163 metabolites could be arranged with metaP (metabolomics Platform) at the Genome Analysis Center (GAC): http://www.helmholtz-muenchen.de/gac-metabolomics/ Metabolites include: amino acids, glycerophospholipides, sphingomyelins and acylcarnithines.

MausDB: the German Mouse Clinic open source phenotype data and mouse management system

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Mutant mouse lines are important tools to elucidate gene function as observed phenotypes can mostly be attributed to a known genotype. The German Mouse Clinic (GMC, http://www.mouseclinic.de) as an open-access platform offers standardized and comprehensive phenotype analysis of mutant mouse lines and screens for potential new mouse models of human diseases. In the GMC, mouse cohorts pass through 14 different screening modules in a strictly defined workflow in the course of primary screen where up to 240 physiological parameters per mouse are measured. Screening many mouse cohorts in multi-parallel workflows is a logistical challenge and requires appropriate IT support and well-defined data infrastructure. Therefore, we developed a web-based database application - MausDB - for the GMC that serves as a central data platform accessible by all GMC users. MausDB supports scheduling of mouse lines to the phenotyping pipelines by work list management functions. Phenotyping data upload to MausDB and re-export is done via spreadsheet files. MausDB also offers standard mouse management functions (breeding support, cage management, etc.) and integrates phenotype data with line/genotype data and other metadata on the individual mouse level. For the GMC, this is a prerequisite for inter-line data analysis, data mining and data exchange in a cross-European phenotyping effort (EUMODIC). Although primarily developed for the GMC, MausDB also proved to be useful for other mouse facilities due to its general purpose design and intuitive user interface. Hence, we offer MausDB to the mouse community as open source software under the terms of the GNU General Public License.

New mouse models and mechanisms for bone and cartilage disorders

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The aim of the Dysmorphology, Bone and Cartilage Screen of the German Mouse Clinic (GMC) is the identification and characterization of mouse models for bone-related human diseases like osteoporosis, osteoarthritis, osteogenesis imperfecta, scoliosis or limb defects. We have implemented an experimental set-up utilizing DXA, X-ray, a 54-parameter protocol for rapid morphological observation of animals, µCT, pQCT, markers of bone metabolism and hormonal regulation, fracture/stress parameters and an osteoblast cell culture system to describe potential cellular causes of bone diseases.
Since the beginning of the GMC the Core Facility provided 85 mutant mouse lines and 16 inbreeding or hybrid lines for the primary screen. Most of the mutant lines have already finished the phenotypic analysis in the Bone and Cartilage module. In 26 mutant lines, a bone specific phenotype was known before the GMC screen, and we could confirm all of them. In 20 lines out of the 26 lines, we were able to detect additional phenotypes. In 15 mutant lines where no bone phenotype was known, we detected new phenotypes. We were able to characterize new mouse models for Osteogenesis imperfecta, inflammatory arthritis, osteoarthritis and osteoporosis. For example, the *Aga2* mutant mouse line represents a new murine model for type II osteogenesis imperfecta. We provide evidence that the *Col1a1*^{Aga2} mutation initiated an ER stress-specific cascade involving caspases 12 and 3 causing apoptosis of osteoblasts. We recently published the *Ali18* mouse mutant line, the first non-induced mouse model for psoriatic arthritis, dermatitis and osteoporosis. *Ali18* mice exhibit rubor and swelling of footpads in hindlimbs in adults. The Dysmorphology, Bone and Cartilage Screen of the GMC is an efficient and powerful platform to identify and characterize new mouse models for bone related human diseases. In our new GMC II an activity platform will be established to test gene-environment interactions on bone health.

EMMA - The European Mouse Mutant Archive

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The European Mouse Mutant Archive (EMMA) offers the worldwide scientific community a free archiving service for its mutant mouse lines and access to a wide range of disease models and other research tools. A full description of these services can be viewed on the EMMA website at http://www.emmanet.org.
The EMMA network is comprised of ten partners who operate as the primary mouse repository in Europe and is funded by the participating institutes and the European Commission Research Infrastructures Programme.

EMMA's primary objectives are to establish and manage a unified repository for maintaining mouse mutations and to make them available to the scientific community. In addition to these core services, the consortium can generate germ-free (axenic) mice for its customers and also hosts courses in cryopreservation.
All applications for archiving and requests for mutant mouse strains are submitted through the EMMA website. Mouse strains submitted for archiving are evaluated by EMMA's external scientific committee. Once approval has been granted depositors are asked to send mice of breeding age to one of the EMMA partners for embryo or spermatozoa cryopreservation. Strains held under the EMMA umbrella can be provided as frozen materials or re-derived and shipped as live mice depending on the customer's needs. However, certain strains that are in high demand are maintained as breeding colonies to facilitate their rapid delivery. All animals supplied by EMMA are classified as SPF in accordance with the FELASA recommendations. EMMA is a founding member of FIMRe (International Federation of Mouse Resources) and actively cooperates with other leading repositories like TJL and the MMRRC in the US and BRC RIKEN from Japan.

The HZI infection challenge platform for mutant mice: development of new models and procedures

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Acute and chronic infections are worldwide one of the major health risk factors. Estimates from the WHO account about 15 million death cases annually directly to infectious diseases, not including mortalities caused by chronic infections or secondary diseases triggered by pathogens. Recent examples of re-emerging and new emerging diseases like SARS and H5N1 influenza A virus infections further underline the global impact that pathogens can impose on human health. In recent years a more detailed understanding of the cellular, molecular and genetic basis of host-pathogen interactions has been gained, but more research is needed to fully understand the host immune response to different classes of pathogens, associated mechanisms of pathogenesis and possibilities to interfere with disease development. We established the mouse "Infection Challenge Platform" (ICP) to specifically investigate immune defects and pathologies in mutant mouse lines (MML) associated with infectious diseases. Supported by the NGFN, the HZI in Braunschweig provides a unique expertise and infrastructure required for specialized infection challenge experiments of MMLs. In the new funding period we will extend our ICP portfolio. Beside our bacterial infection models we introduce a mouse-adapted H1N1 Influenza A virus strain as a new pathogen. Using the ICP analysis tools we want to identify new host factors contributing to the severe pathology of influenza infections, gain a better understanding of viral pathogenicity and identify prognostic indicators of severe influenza pathogenesis. Further we will extend our recently established model of orally induced listeriosis by developing a bioluminescent *L. monocytogenes* strain. An *in vivo* imaging system will be used to characterize non-invasively the course of infection in cohorts of mutant and wild-type mice. Using this technology we can address questions regarding the dissemination of *Listeria* from the natural site of infection to the target organs.

The pathology screen in the German Mouse Clinic

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Introduction: Experts from various fields of mouse physiology analyse genetically engineered mice side by side in the GMC. This detailed analysis is completed by the pathology screen that is conceived to provide a complete morphologic phenotype of mouse models to support discovery of gene functions and to disclose the pathways and processes through which these genes influence the development of human diseases.

Materials and Methods: In the so called primary screen the mice are dissected and macroscopically examined; all their organs are analysed histologically (H&E). In the secondary and tertiary screen the mice can be analyzed in more detail using auxiliary techniques such as x-ray, immunhistochemistry, electron microscopy or molecular methods. During the last years we have analysed the most used inbred mouse strains (C3H, B6, Balb/C, 129) to standardize morphological variations.

Results: We found a lot of strain- and sex-specific differences, e.g. lack of the corpus callosum in 39% of the Balb/C mice and in 60% of the 129 strain, prominent MALT and BALT in the C3H strain or higher susceptibility (61%) to develop liver microgranulomas in B6 mice.

Conclusion: Strain-specific morphological variations could, if unknown, lead to wrong conclusions. The knowledge of these variations helps to minimize possible mistakes in the interpretation of data and to perform a systematic phenotype of genetically engineered mice.

New database-driven tools for cryo sample and workflow management

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The Cryo Unit of the Helmholtz Centre Munich, Institute of Experimental Genetics is one of the nodes of the European Mouse Mutant Archive (EMMA). Among others its main objectives are cryo-archiving of mutant mouse lines as sperm or embryos and re-derivation of frozen samples. Typically, numerous long projects are processed in parallel. In a high-throughput cryo lab, managing the logistical aspects of work planning and division of work in a team is a key factor for efficient work and animal welfare. Central, standardized management of sample properties and sample storage locations are essential aspects of reliable data storage and data exchange with partners inside and outside the EMMA consortium. Therefore in close collaboration with the Cryo Unit we have developed two database-driven web applications for cryo workflow management and sample archiving, called CryoDB and TankDB. CryoDB stores information about mouse lines and collaboration partners and handles individual cryo-archiving workflows, their single work steps, deadlines and responsibilities for the tasks. A modular, hierarchical system of selectable cryo workflows supports the users in keeping track of the next tasks and reporting all results and task status changes visible for all users. Reminders sent via email a few days before a task deadline is reached help meeting the deadlines. TankDB manages any kind of sample type, storage container and an indefinite number of sub-containers. Samples can be divided into aliquots with any attributes (e.g. sperm quality, no. of embryos per straw, etc.). The system supports the users in splitting samples for backup reasons and finding empty storage slots for new samples. Both applications offer generation of reports and overviews to increase usability. While CryoDB is in use for almost 2 years, TankDB will commence operation by the end of the year. Both applications will be released as open-source software after publication.

Superoxide dismutase 3, extracellular (SOD3) and lung function in mice

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Rationale: Diminished lung function and impaired lung development are associated with increased susceptibility to chronic obstructive pulmonary disease (COPD) and asthma. However the genetic determinants of lung function development are not well known. Our genome-wide analysis of C3H/HeJ (C3H; normal lung function) and JF1/Msf (JF1; limited lung function) mice previously identified *Sod3* as a candidate for increased dead space volume (V_D) of the conducting airways in JF1 mice. Because SOD3 is the primary extracellular antioxidant of lung and is known to protect the extracellular matrix (ECM) from lung injury, we sought to investigate the SOD3 transcript and protein expression in these strains and to evaluate the functional consequence in gene targeted *Sod3*$^{(-/-)}$ mice

Findings: Sharp decline of *Sod3* between postnatal days 14-28 was detected in JF1 lung, which is the peak phase of alveologenesis in mice. Single nucleotide polymorphisms in the *Sod3*^{JF1} promoter region were identified within core sequences of putative transcription factor binding sites that could account for the lowered *Sod3*. *In-situ* hybridization/immunohistochemistry revealed that SOD3 mRNA and protein levels were reduced in airway epithelial cells, type II alveolar cells and their associated matrix of JF1 lung. Gene-targeted *Sod3*$^{(-/-)}$ mice had increased V_D (female:254±4µl; male:258±3µl) compared to that of sex-matched *Sod3*$^{(+/+)}$ mice (female:228±2µl; male:230±3µl). This is consistent with our previous findings in JF1 mice.

Conclusions: SOD3 is a determinant of V_D in mice. Diminished SOD3 during lung development may limit lung function by reducing ventilation efficiency.

Metabolic phenotyping of an obese mutant mouse line

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The Metabolic Module of the German Mouse Clinic (GMC) performs a comprehensive analysis of energy balance in mouse mutants. It is based on the conflation of different methods for the investigation of disturbances in body weight regulation, energy metabolism and body composition. We investigated an obese mutant mouse line generated and identified in the recessive screen of the Munich ENU Mutagenesis project. This mutant line is the heaviest line phenotyped since the start of the Metabolic Module (+ 14.3 g in males and + 16.8 g in females compared with controls). When categorised into body mass classes of F1 outcrosses on C57BL/6 background at the age of 14 weeks, a clear separation into two subpopulations indicates that the overweight phenotype is heritable. Chemical carcass analysis shows that fat mass is significantly increased whereas lean mass is slightly decreased in mice labelled as mutants. Metabolised energy per mouse does not differ between mutants and controls under regular housing conditions. At an ambient temperature of 24 °C, daily energy expenditure also does not differ between mutants and wildtypes. However, resting metabolic rate of mutant mice is lower than expected for the respective body weight.
In mutant mice higher blood glucose levels under ad libitum conditions indicate diabetes. Fasted plasma glucose is increased and glucose clearance during an intraperitoneal glucose tolerance test decreased in mutant mice. They also show a significantly higher concentration of ALT which could be an indication of a fatty liver. The values of total cholesterol as well as HDL are significantly increased whereas LDL is only slightly increased. Currently, substantial efforts are made to identify the affected gene by SNP mapping and QTL analysis. The obtained findings in physiological variables suggest that the mutant line could be a new model for the metabolic syndrome.

A comprehensive approach to identify early derangements in metabolic pathways involved in type 2 diabetes pathophysiology in mouse models

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Type 2 diabetes mellitus is among the most frequent chronic metabolic disorders and incidence is worldwide rising due to population ageing and increasing obesity associated with sedentary lifestyles and changes in nutritional habits. To develop effective strategies for diabetes prevention and treatment, novel approaches for the elucidation of disease-relevant molecular pathomechanisms are required. To explore diabetes aetiology it will be crucial to study intricate biological systems - as these consider multiple interactions of genes, pathways, and tissues - throughout disease progression. In mouse models associations of genes or point mutations (e.g. transgene/knockout mice, Munich ENU mutagenesis program-derived mutants) with clinical phenotypes allow for systemic correlations and determination of co-susceptibilities between diabetes and other diseases. Thus, mouse mutants are subjected to comprehensive phenotyping in the German Mouse Clinic (GMC) covering 14 diseases areas. When Primary Screens reveal traits of interest in a particular mouse model, the "Diabetes Screen" will apply specialised techniques (e.g. glucose clamps) to localise primary, organ-specific defects such as pancreatic □-cell dysfunction or blunted insulin action in insulin target tissues. Pleiotropic interactions between genetic disposition and environmental context modulating diabetes onset and progression will be further investigated in the GMC II by applying e.g. nutritive or exercise challenges. The acquired multidimensional, phenotypic informations in context with alterations in spatio-temporal and quantitative metabolomic patterns, assessed in collaboration with the HMGU Metabolomics Platform, will be used to identify novel pathways implicated in the progression from a healthy to a diseased state and contribute to more effective diagnostic, preventive, and personalized therapeutic strategies.

Neurological and molecular biological characterization of the mutant mouse line Tom40, the protein that comprises the general import pore of mitochondria

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Mitochondria provide cellular energy by oxidative phosphorylation. Defects of energy metabolism are involved in a variety of human diseases. These disorders manifest preferentially in tissues with high aerobic demand such as brain and muscle. Mutations in genes for mitochondrial proteins are known to be causative for several diseases. Furthermore mitochondrial dysfunction is currently discussed as a key player in neurodegeneration and aging. The vast majority of mitochondrial proteins is encoded by nuclear genes and then imported into the organelle. By gene trap mutagenesis, we have created knockout mouse models for several genes of the mitochondrial import machinery. The TOM (translocase of outer mitochondrial membrane) complex mediates the import of all proteins of mitochondria into the intermembrane space and additional the insertion of proteins into the outer membrane. Tom40 comprises the main component of the TOM complex as it forms the general import pore. Homozygous *Tom40*-/- mice are not viable. Heterozygous *Tom40* +/- mice showed no differences in locomotor activity, muscle force and motor coordination. We could not observe a clinical neurological phenotype. Our next steps will include an exact characterisation of the insertion site of the gene-trap vector and expression analysis on protein and mRNA level in different tissues. Additionally, we will perform challenging experiments and embryo/blastocyst stainings in order to find out at which time point *Tom40*-/- animals die. The analysis of this mouse model of mitochondrial import will lead to a better understanding of this essential pathway in mammals.

Infrafrontier - the European infrastructure for phenotyping and archiving of model mammalian genomes

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Mouse models are essential tools for the functional analysis of the mammalian genome and the molecular basis of human diseases. The European research community and international collaborative efforts such as the International Mouse Knockout Consortium (IMKC) will produce a large number of mouse disease models over the next years. The bottleneck for the exploitation of this valuable resource will be access to systematic functional and molecular characterisation. In addition, mouse models should be made available to the entire European mouse genetics, biomedical and translational research community, which strongly depends on access to novel mouse disease models. The current resources to achieve this goal are limited. Existing facilities across Europe can only offer capacity for the systemic phenotype analysis, archiving and dissemination of a few hundred disease models per year. To solve this problem, the Infrafrontier project will organise and establish an efficient distributed infrastructure for the systemic phenotyping, archiving and distribution of mouse models on a well-concerted, large-scale and pan-European level. Infrafrontier will organise two complementary and linked European infrastructure networks: Phenomefrontier for large scale and comprehensive phenotyping in a cross-laboratory effort (European mouse clinics); Archivefrontier for archiving and distribution of mouse mutant lines (organised by EMMA, the European Mouse Mutant Archive). Taken together, Infrafrontier will bring the systemic phenotyping, archiving, and dissemination of mouse disease models to the next level and will contribute to maintaining Europe's leading role in the functional annotation of the mouse genome. Infrafrontier has been included in the roadmap of the European Strategy Forum for Research Infrastructures (ESFRI) and receives Preparatory Phase funding by the European Commission.

Uromodulin-storage disease in an ENU-induced mutant mouse line

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Uromodulin (Tamm-Horsfall protein) is expressed kidney-specifically and represents the most abundant urinary protein in mammals. Although the protein was already identified in 1950, it's function is still unclear. It was demonstrated, that uromodulin has a protective effect against ascending urinary tract infection. In addition, it is involved in the pathogenesis of cast nephropathy, urolithiasis, and tubulointerstitial nephritis. Uromodulin might also affect creatinine clearance and urinary concentration ability. Mutations of the uromodulin (Umod) gene in humans cause various renal diseases which are summarized as uromodulin-storage disease. Within the Munich ENU mouse mutagenesis project, a nephropathic mutant mouse line was established harbouring a recessive mutation within the Umod gene. In-depth analyses were performed to elucidate the consequences of the mutant uromodulin protein on kidney function. The mutant mouse line exhibits many features described for the uromodulin-storage disease in humans. In addition, further aspects of the mutation like the effect on energy metabolism and body composition were detected.

Comparative histology of inflammatory bowel diseases (IBD) in mice: TNFdARE mutant and Interleukin-10 knockout and mice

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Introduction: Human Crohn's disease (CD) and ulcerative colitis (UC) cause significant morbidity, but the etiology remains still unknown. A variety of mouse models have been created: Interleukin-10 homozygous knockout mice develop chronic enterocolitis similar to human UC, and TNFdARE heterozygous mutants a CD-like IBD. For comparative purposes, it was our goal (1) to evaluate the validity of these models compared to human diseases, and (2) to evaluate the suitability of different histological scoring systems.
Material and methods: Histology was performed in 130 TNFdARE and 80 Il-10 mutant mice. The intestinal segments (FFPE) were stained with H&E, PAS, trichrome, alcian blue, and IHC (CD3, B220, CD79, CK, Ki67, p53) was performed.
Results: TNFdARE mutants develop ileocolitis. Inflammatory mucosal cell infiltration (CD3+ T-cells) progresses transmural. Associated epithelial damage includes villus blunting, crypt loss and abscesses. Additionally, cryptal hyperproliferation, goblet cell loss, and minimal fibrosis are observed. Ulcer or fissures are rarely, and granulomas are not found.

Il-10 deficient mice are affected by colitis and typhlitis. The mixed inflammatory cell infiltrates rarely invades the muscularis. Prominent crypt abscesses are present - sometimes accompanied by marked stromal reaction. Epithelial damage ranges from small erosions to severe ulceration. Hyperplasia is characteristically present and often focal dysplasia.

Discussion: Many characteristics of human CD are present in the TNFdARE mutants. Significant differences to man are the lack of fibrosis, granulomas, and fissuring. Il-10 knockout mice show a high similarity to human UC, including mucosal atrophy / regeneration, and crypt abscesses. The appearance of dysplastic foci additionally provides the possibility to study IBD-associated carcinogenesis. In conclusion, both murine IBD models provide models to study the pathomechanism and new therapeutic strategies.

Proteasomal inhibition reduces *parkin* mRNA in PC12 and SH-SY5Y cells

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Mutations in the gene encoding the E3 ubiquitin-protein ligase parkin have been shown to be a common genetic cause of familial early-onset Parkinson's disease (PD). In addition to its function in the ubiquitin-proteasome system (UPS), parkin has been ascribed general neuroprotective properties. Stress and mutation induced decreases in parkin solubility leading to compromised cytoprotection have recently been reported. We systematically investigated whether PD-related stresses including MG132 and epoxomicin (proteasomal impairment), tunicamycin (unfolded protein stress), and rotenone (mitochondrial dysfunction) resulted in expressional changes of *parkin* and other E3 ubiquitin ligases (*dorfin*, *SIAH-1*). Rotenone and tunicamycin did not change *parkin* mRNA levels, whereas proteasomal inhibition resulted in a reduction of *parkin* mRNA in PC12 cells as well as in SH-SY5Y cells. Therefore, surprisingly, cells did not react with a compensatory *parkin* upregulation under proteasomal inhibition, although, in parallel, parkin protein shifted to the insoluble fraction, reducing soluble parkin levels in the cytosol. Since the mRNA of the parkin-coregulated gene *PACRG* paralleled the *parkin* mRNA at least partly, we suspect a promoter-driven mechanism. Our study therefore shows a link between proteasomal impairment and *parkin* expression levels in cell culture, which is intriguing in the context of the described and debated proteasomal dysfunction in the substantia nigra of PD patients.

Regulation of astrocyte inflammatory responses by the parkinson's disease -associated gene DJ-1

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Mutations in the *DJ-1* gene cause autosomal-recessive Parkinson's disease (PD). In addition to neuron-intrinsic protective functions, its up-regulation in reactive astrocytes also suggests a glial contribution of DJ-1. Here we show in astrocyte-rich primary cultures derived from *Dj-1* knockout mice that DJ-1 regulates pro-inflammatory responses. When treated with the bacterial endotoxin lipopolysaccharide (LPS) as well as the PD-linked protein alpha-synuclein, *Dj-1* knockout astrocytes generated >10 times more nitric oxide (NO) than littermate controls. The excessive NO production was a direct consequence of *Dj-1* ablation, because lentiviral reintroduction of DJ-1 specifically restored the NO response to LPS. Enhanced NO production in *Dj-1* knockout astrocytes was mediated by hyper-stimulation of type II NO synthase (iNOS). In addition to iNOS, *Dj-1*$^{-/-}$ astrocytes also induced stronger cyclooxygenase-2 and interleukin-6, all pro-inflammatory mediators implicated in PD pathogenesis. These effects coincided with phosphorylation of p38 mitogen-activated protein kinase (MAPK), and inhibition of this pathway with SB203580 suppressed NO production and iNOS induction. Moreover, enhanced phosphorylation of p38^{MAPK} was detected in DJ-1 deficient *Caenorhabditis elegans* exposed to pathogenic gram-negative bacteria (*Pseudomonas aeruginosa*), which stimulates LPS-dependent p38^{MAPK} signaling in *C. elegans*. Finally, primary neuron cultures grown on *Dj-1* knockout astrocytes were significantly sensitized to LPS, directly demonstrating the neurotoxic potential of DJ-1 deficiency in astrocytes. Collectively, our findings identify DJ-1 as an evolutionary conserved regulator of pro-inflammatory responses and suggest that loss of DJ-1 contributes to PD pathogenesis by deregulation of astrocytic neuroinflammatory damage.

Differential proteome analysis of transgenic A53T-alpha-synuclein mice as a model of familial Parkinson's disease

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Parkinson's disease (PD) is a severely disabling neurodegenerative disorder at old age of unknown cause. The neuropathological hallmark is the loss of dopaminergic neurons which project from the substantia nigra pars compacta to the striatum. Within affected neurons the pathological process is reflected by abnormal protein aggregates, so called Lewy bodies (LB), which consist mostly of the presynaptic chaperone □-synuclein. Various mutant forms of □-synuclein, most importantly the A53T-mutation, have been demonstrated to cause early-onset PD with autosomal dominant inheritance. Recently, a mouse model with transgenic expression of human A53T-□-syn cDNA in the dopaminergic nigral neurons was established to model early pathological events of PD pathogenesis. A reduction of spontaneous locomotor activity and a diminished striatal response to dopaminergic innervation in this mouse indeed reflect classical features of PD, but the molecular basis of this pathology is not understood. To elucidate early and late effects of A53T-□-syn on the protein network mediating dopaminergic neurotransmission we investigated striata of 6 months and 22 months old transgenic mice. We applied two-dimensional fluorescence difference gel electrophoresis (2D-DIGE) to monitor changes in protein expression levels and mass spectrometry to identify the dysregulated proteins. At 6 months our data show an altered mitochondrial respiration and the up-regulation of the protein 14-3-3 □, which is a modulator of the dopamine synthesis enzyme tyrosine hydroxylase. In 22 months old mice the persistent overexpression of 14-3-3 □ is aggravated by up-regulation of glial fibrillary acidic protein, suggesting astrogliosis in compensation to neurodegeneration.

Strategies for biomarker discovery - from differential expression to metabolites to pathways

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A major goal in the area of psychiatric disorders is the identification of biomarkers that can categorize subsets of subjects in a more reliable and consistent manner. We have developed strategies that combine genetic, proteomic, enzymatic and metabolite analyses in a robust and valid animal model of trait anxiety to identify pathways pertinent to the disease phenotype. Components of the identified disease related pathways resulting from such analyses have been implicated in the pathobiology of psychiatric disorders. We submit that follow up studies including metabolite and enzymatic assays relevant for pathways implicated by proteomic analysis add great value to biomarker identification efforts. This strategy is particularly relevant for translating results obtained in animal models to the clinic. Since the same protein expression difference identified in the mouse model may not necessarily be associated with the relevant patient phenotype, it is far more promising to interrogate the pathway that a protein marker is a part of. This information can illuminate possible dysfunctions causing the disease phenotype in patients. Examples for this strategy and experimental approaches addressing protein turnover rates by stable isotope metabolic labeling of mouse models will be outlined. Experimental data from *in vivo* metabolic labeling provide a powerful platform for pathway analysis as it relates to disease phenotypes.

Functional validation of P2RX7 as a susceptibility marker for depression using humanized mouse mutants

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Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BP) are the most common psychiatric disorders with a combined lifetime prevalence of about 15%. Recent linkage and association studies suggest P2RX7 as a novel susceptibility gene for MDD and BP. A non-synonymous SNP located in exon 13 has been shown to be associated with reduced calcium influx and is likely to affect P2RX7 oligomerization and protein-protein interactions. To study the functional relevance of the polymorphism in an appropriate *in vivo* model we will generate and characterize humanized mouse mutants in which the murine P2RX7 is substituted by the human P2RX7 gene. A knock-in approach based on homologous recombination in embryonic stem (ES) cells was used to generate mutant mice expressing either the wild-type or the mutant, disease-associated isoform of human P2RX7. ES cell clones were screened by Southern Blot analysis. Positive clones were injected into blastocyts and chimeric animals were screened for germline transmission by PCR. The expression of human P2RX7 mRNA was analyzed by *in situ* hybridization (ISH) using a probe specific for human P2RX7. In case of the mutant variant of human P2RX7 we obtained two correctly recombined ES cell clones. Using these clones for blastocyst injection we obtained in total 24 chimeras. In terms of the wild-type variant we identified four positive clones which resulted in a total of 23 chimeras. In both cases the humanized P2RX7 allele was transmitted through the germline. The correct expression of the human P2RX7 variants in the brain of heterozygous mutant animals was confirmed by ISH. Using these humanized mouse lines, we will be able to validate the potential of P2RX7 as a susceptibility marker for MDD and BP in an animal model. The future analyses will involve molecular, endocrinological, electrophysiological and behavioural paradigms to characterize the functional impact of the polymorphism in detail.

Behavioral changes in G72/G30 transgenic mice

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Genetic studies have implicated the evolutionary novel, primates-specific gene locus G72/G30 in schizophrenia, bipolar- and panic-disorders. It encodes for a protein LG72 whose function has been controversially discussed as putative regulator of the peroxisomal enzyme D-amino-acid-oxidase (DAO), or as a mitochondrial protein, which promotes robust mitochondrial fragmentation in mammalian cell lines including human and rat primary neurons. Because of this conserved function we here have generated "humanized" BAC transgenic mice (G72Tg) expressing alternatively spliced G72 and G30 transcripts, and the LG72 protein. G72 expression is prominent in granular cells of the cerebellum, the hippocampus, the cortex and the olfactory bulb. Most strikingly, G72Tg mice displayed deficits in sensorimotor gating which could be reversed with haloperidol, increased sensitivity to PCP, motor-coordination deficits, increase compulsive behaviors and deficits in smell identification. These results demonstrate that expression of the human G72/G30 gene locus in mice produces behavioral phenotypes that are relevant to psychiatric disorders.

Perturbation of oncogenic signalling and transcriptional control - an integrated study combining RNA interference and expression profiling

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The Ras signaling pathway plays a decisive role in many types of human and experimental cancer. Many growth factor pathways converge on Ras proteins. These proteins serve as molecular switches that couple extracellular signals with the transcriptional machinery. Chronic Ras pathway activation is mediated by enhanced receptor tyrosine kinase activity, mutational activation of Ras proteins or by genetic alterations in downstream effectors. Mutated forms of Ras proteins serve as biomarkers that permit distinguishing non-responders from responders in receptor-targeted therapy. However, the predictive value of wild-type Ras function is restricted to subgroups of cancer patients only. Therefore, it is essential to understand the structural organization, biological/clinical function and regulation the Ras signalling system in detail and to dissect its long-term impact on the genetic program. Gene expressing profiling contrasting Ras oncogene-transformed and normal precursor cells has yielded heterogeneous results so far. To dissect the functional relationship between Ras signalling pathways and the genetic program, we are using an integrated approach combining expression profiling, computational methods for predicting transcription factors involved in target gene deregulation and pharmacological or siRNA-mediated pathway perturbation with chromatin-based and cellular assays. In this way, we were able to elucidate the functional effect of individual signalling kinases and deregulated transcription factors on the transcriptome and on phenotypic properties in mesenchymal and epithelial cell systems. The same experimental strategy was also helpful to identify robust transcriptional changes in Ras-expressing cells and to distinguish them from putatively secondary changes.

Identification of novel effector genes for malignant melanoma via recombinant cancer cell technology

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Human malignant melanoma is a highly aggressive and drug resistant cancer type, the incidence and mortality of which steadily has been increasing world wide. In order to get more insight into the key underlying molecular events, which have not been clearly elucidated yet, we have developed a powerful recombination-based system to generate libraries of stably transfected cell lines. By integrating genes of interest into a defined recombination site, we are able to generate highly standardized series of isogenic cell lines. We performed a functional screen in melanoma cells using the described technology. An initial analysis of ~ 120 recombinant isogenic melanoma cell lines, inducibly overexpressing potential cancer candidate genes, identified 22 genes strongly affecting the cancer cell viability. Further validation studies showed a tumor suppressive effect of one of the effectors also in other tumor types as well as deregulated expression levels in corresponding tumor and normal tissues.

After having demonstrated the applicability of the technology, it will now be utilised within the NGFN projects IG-Proceed and IG-Mutanom. As part of the project IG-Mutanom, we will perform a detailed functional analysis with regard to cancer-relevant parameters of mutated cancer proteins in comparison to their normal counterparts in various tumour types. These studies aim at elucidating the consequences of mutations frequently identified in various tumor types, which should give rise to novel targets for innovative diagnostic and therapeutic strategies.

Construction and use of recombinant isogenic cell libraries in functional genomics

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While nowadays robotics enables to perform whole genome functional screens within a few days only, the availability of suitable cellular systems to investigate the function or pathway of choice evolves as a major bottleneck. In most applications, it is desirable to use cell lines with stably inserted reporter systems or over expression/silencing of a target gene. We developed a simple recombination-based system, which allows to serially introduce genes or RNAi-constructs into cancer cell lines. This method yields highly standardized (isogenic) stable cell line libraries with hyperactivation or inactivation of a gene of choice in a constitutive or tetracycline-inducible fashion. We also provide proof-of-principle that this technique can be used for the construction of double recombinant cell lines, which allows for analyses at advanced levels of complexity, e. g. by the construction of double reporter systems.

In a pilot experiment, we constructed a library consisting of about 120 isogenic melanoma cell lines, in which each individual clone over expresses a different cancer candidate or control gene in a tetracycline-inducible fashion. An initial screen identified 22 genes with substantial effects on cancer cell viability. We further validated three of these genes, which represent one tumor suppressor and two oncogenes for various cancer types, such as melanoma, brain, breast, and lung cancer. These techniques are now projected to systems biology, drug target identification, and high-throughput functional genomics approaches within IG-Prostate Cancer, IG-MUTANOM, and D*A*Nomics, which represents a new Danish "omics" research initiative that is in the process of being assembled.

Identification of neuroblastoma stem cells

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Background: The cancer stem cell (CSC) hypothesis suggests that rare multipotent cells with indefinite potential for self-renewal drive the onset and growth of tumors. Although the existence of CSCs in leukemia and some solid tumors is established, CSCs have not yet been clearly identified in neuroblastoma (NB). NB cells should qualify as NB-CSCs if they are characterized by long-term self-renewal, multipotency, generation of many progeny and NB-initiating ability upon serial transplantation into mice.

Methods and Results: To evaluate if NBs contain cells capable of long-term self-renewal under conditions that promote expansion of adult neural stem cells, 13 fresh post-surgery primary NBs and 2 NB metastases from bone marrow of consenting patients were dissociated and plated at low density into the neurosphere assay. To assess the number of primary neurosphere-forming cells, a primary sphere formation assay was performed. The frequency of neurosphere-forming cells ranged between 0.01% and 0.5% and correlated with clinical poor prognostic factors such as amplified *MYCN* and INSS stage 4. Next, we performed limited dilution assays. In contrast to primary neurospheres derived from stage 4S-NBs without amplified *MYCN*, neurospheres of stage 4 NBs with amplified *MYCN* were expandable for many passages resulting in the generation of clonal cell lines. To investigate the phenotypes of these cells, protein expression of neural stem cell markers was assessed using flow cytometry. The number of cells positive for these markers ranged between approximately 2% and 20%. To elucidate the NB-initiating ability *in vivo*, cells were implanted into mice. Compared with established NB cell line-derived tumors, NBs developed at both lower seeding density and much slower rate.

Conclusions: Both primary NBs and metastases contain a minor cell fraction capable of long-term self-renewal *in vitro*, which expresses neural stem cell markers and gives rise to tumors *in vivo*

The development of a new murine *MYCN* overexpressing neuroblastoma cell line

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Neuroblastoma is the most common solid extracranial tumor in childhood. High-level expression of MYCN plays an important role in maintaining the malignant phenotype of neuroblastoma and is the most important clinical marker for poor prognosis. The *MYCN* oncogene is amplified in more than 40% of patients with advanced disease. For these patients the development of new therapeutic strategies is desperately needed. Recent studies suggested that *MYCN* is a suitable target for immunotherapy, but up to now, a syngeneic neuroblastoma mouse model overexpressing *MYCN* is not available to examine therapeutic strategies *in vivo*. Here, we report the establishment of a *MYCN* overexpressing murine neuroblastoma cell line syngeneic to A/J mice. For this purpose, the murine neuroblastoma cell line NXS2, which is derived from A/J mice and shows a low MYCN expression, were stably transduced with the *MYCN* cDNA by a lentiviral vector system. Stable transduction was verified by real-time PCR and Western-Blot, revealing significantly higher expression levels of MYCN compared the human *MYCN*-amplified cell line Kelly, which contains about 120 copies of the *MYCN* gene. Additionally, the expression of the new NXS2-MYCN cells is about 25 fold higher than in wildtype NXS2 cells. Characterization of the murine *MYCN* expression cells *in vitro* and *in vivo* will be reported. In summary, we report the development of a new murine *MYCN* neuroblastoma cell line providing an important new syngeneic mouse model for the *in vivo* evaluation of new therapeutic strategies for this highly aggressive type of neuroblastoma.

Transcriptional upregulation of $Ca_V3.2$ mediates epileptogenesis in chronic epilepsy

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In both humans and animals, an insult to the brain can lead, after a variable latent period, to the appearance of spontaneous epileptic seizures that persist for life. The underlying processes, collectively referred to as epileptogenesis, include multiple structural and functional neuronal alterations. We have identified the T-type Ca^{2+} channel $Ca_V3.2$ as a central player in epileptogenesis. We show that a transient and selective up-regulation of $Ca_V3.2$ subunits on the mRNA and protein levels after status epilepticus (SE) causes an increase in cellular T-type Ca^{2+} currents and a transitional increase in intrinsic burst-firing. These functional changes are absent in mice lacking $Ca_V3.2$ subunits. Intriguingly, the development of neuropathological hallmarks of chronic epilepsy, such as subfield specific neuron loss in the hippocampal formation and mossy fiber sprouting, was virtually completely absent in $Cav3.2^{-/-}$ mice. In addition, the appearance of spontaneous seizures was dramatically reduced in these mice. Together, these data establish transcriptional induction of $Ca_V3.2$ as a critical step in epileptogenesis and neuronal vulnerability.

Kv7/M-type potassium channels are critical determinants of neuronal network activity in neonatal mouse brain

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To investigate pathophysiological mechanisms underlying brain developmental abnormalities and epileptogenesis linked to Kv7/KCNQ/M-type potassium channel deficiency that is associated with a neonatal epilepsy syndrome in humans, we generated transgenic mice with attenuated M channel activity. Tet-Off system-mediated restriction of transgene expression to defined developmental periods revealed a critical role for M channels in neonatal brain development. Suppression of M channels during this period resulted in a severe phenotype that included neurodegeneration and neuroinflammation in the hippocampus, increased seizure susceptibility, spontaneous epilepsy, and marked behavioral changes. We hypothesized that attenuated M-channel activity causes changes in neuronal network activity in neonatal brain. Therefore, we performed simultaneous acute depth profile recordings of local field potentials and unit activity in visual cortex (V1) and hippocampus in awake head-fixed P5-7 pups. V1 network activity in control mice consisted of short spindle-like bursts in superficial layers with frequencies in the beta2 range (10-30 Hz). Activity in the hippocampal CA1 region mainly consisted of sharp waves with maximum amplitudes in stratum radiatum and phase reversal in the pyramidal cell layer reflecting Schaffer collateral activation. In V1 of mutant mice spindle burst were more frequent and increased in frequency, amplitude and duration.Acute treatment with the NKCC1 blocker bumetanide that lowers $[Cl^-]_i$ in immature neurons reduced cortical and hippocampal network activities and specifically suppressed spindle bursts in V1. Chronic bumetanide treatment during the first two neonatal weeks prevented morphological hippocampal changes and improved the behavioral phenotype to comparable levels as did doxycycline-suppressed transgene expression. The data suggest that cortical M-channels are critical for the control of network oscillations in the neonatal mouse brain.

Characterization of novel prostate cancer genes by targeted functional genomics

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Microarray analyses of global changes in gene expression patterns have recovered a large number of genes, which are deregulated in prostate cancer, when compared to a normal prostate tissue. In order to successfully translate these data into clinical intervention strategies, it is crucial to determine genes that truly contribute to tumor development (which may be referred to as 'driver genes') and to separate them from the majority of secondary anomalies in expression levels ('passenger genes').

To achieve this, we construct a library of recombinant prostate cancer cell lines stably overexpressing candidate genes selected from our expression profiling data. In the first step, open reading frames are cloned into Gateway-compatible, tetracycline-inducible expression vector. In parallel, acceptor cell lines are generated from established cancer and normal prostate cell lines by stable integration of a plasmid carrying a recombinase target sequence. After a well-characterized acceptor clone has been obtained, it is expanded into a library of expression clones by parallel insertion of expression vectors mediated by site-specific recombination. This technology has two main advantages:

1) analyzed genes are inserted into a predefined, transcriptionally active locus,
2) the influence of genetic background is minimized, since all clones generated within such library differ only by a presence of the respective gene of interest. In contrast to traditional knock-in strategies, this approach ensures that readily interpretable phenotypes are obtained and thereby provides a highly standardized resource for functional gene analysis. The initial assay involves viability screening of the library. The most promising effectors from the primary screen will be subjected to an expanded range of functional assays, addressing their impact on cell cycle and apoptosis. This strategy will serve as a starting point for an individual characterization of novel prostate cancer genes.

Towards a molecular description of cardiovascular and metabolic disorders in experimental rat models

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The rat genome sequence, including genetic and structural variation maps, provide exceptional opportunities for identifying genes and pathways underlying disease phenotypes. We have devised a general approach for dissecting genetic networks systematically across the biological scale using segregating rat populations. We combined linkage analyses with genome-wide expression profiling and identified independent genes contributing to heart failure susceptibility, increased left ventricular mass, and hypertension in spontaneously hypertensive rats (SHR) and SHR derived substrains. We study the genetic regulation of gene expression in a range of insulin sensitive tissues including fat, kidney, adrenal, heart, skeletal muscle, the vasculature, and liver in rat RI strains. Using the data collected across multiple tissues we can now detect the genotype dependent co-expression of gene networks and suggest their possible biological implications for common cardiovascular disorders.

Within an international collaboration we started to sequence the SHR genome using paired-end sequencing technique on the Solexa platform. Nearly 387 million reads (13.7 GB) were sequenced of which 83% of reads were mapped to the reference BN genome using the MAQ, giving 4.5x coverage of the SHR genome. We identified 2.3 million high quality SNPs and 800,000 indels (1 to 5 bp) between SHR and BN with a very low false positive rate (< 1%). More than 60% of the identified SNPs were novel. We investigated the SNP frequency in promotor regions of cis-eQTL genes which show cis-genetic linkage in the BXH/HXB RI strains and found that the promotor regions of cis-eQTL genes are enriched with SNPs compared to non cis-eQTL genes. Various structural variations (SVs) were identified, and validated in a subset, including insertions, deletions and inversions. Together, these findings will greatly accelerate identification of genomic changes underlying hypertension and other complex phenotypes in the SHR strain.

The zebrafish as a convenient animal model to study repolarization disorders

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Sudden cardiac death especially in the young is predominantly caused by gene mutations in ion-channels that control cardiac depolarisation and repolarisation. However, detailed characterization of the underlying molecular mechanisms, indispensable for more reliable prognosis and for the development of novel therapeutic approaches, is often hindered by the lack of appropriate genetic animal models that display action potential and most notably repolarization characteristics comparable to human cardiomyocytes. The murine heart, for instance, beats 7-10 times faster than the human heart and thereby, especially cardiac repolarization relies on different and incomparable cardiac ion-channels.The most common repolarization disorder is the "long-QT syndrome" (LQTS). Here we show that the electrophysiological features resembling human LQTS in zebrafish mutant *breakdance* is caused by a combinatory effect of impaired trafficking and particularly decelerated ventricular repolarization induced by a partial loss-of-function mutation in the zebrafish *ether-à-go-go-related* gene (zERG) potassium channel. As a result, affected fish display perturbed atrio-ventricular conduction and thereby atrio-ventricular block. Additionally, by utilizing a forward genetics approach we isolated the zebrafish mutant *reggae*, displaying phenotypic features of the recently described human malignant arrhythmia syndrome "short-QT syndrome", like accelerated cardiac repolarization and atrial fibrillation. We identified a missense mutation within the zERG potassium channel, which induces a gain-of-function effect due to defective activation and inactivation kinetics. As a consequence, electrocardiogram recordings taken from *reggae* mutant adult fish display a significant shortening of the QT interval. Our data clearly demonstrate, that zebrafish represents a valuable animal model to further decipher the underlying molecular mechanisms involved in the pathogenesis of repolarization disorders in humans.

Deficiency for Calsarcin-2 increases exercise capacity in vivo by calcineurin/NFAT activation

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Endurance capacity is fundamentally based on the available amount of oxidative skeletal muscle fibers. This fiber type composition is tightly regulated to adapt to changing environmental demands. The phosphatase calcineurin and its downstream targets, transcription factors of the NFAT family, play a critical role in this process via promoting the formation of slow-twitch, oxidative fibers. Calcineurin binds to calsarcins, a family of striated muscle-specific proteins of the sarcomeric z-disc. We hypothesized that genetic ablation of the fast-twitch muscle isoform calsarcin-2 (CS2) might alter calcineurin signaling and, in consequence, fiber type composition of skeletal muscles. After successful genetic targeting of CS2, knockout mice were subjected to physiological, morphometrical and molecular analyses. Mice deficient for CS2 revealed a significantly reduced body weight (-11.9%, p=0.0017) and fast-twitch muscle mass (m. gastrocnemius, -24.4%, p< 0.0001) in the absence of an overt myopathic phenotype. Remarkably, in voluntary exercise studies CS2 knockout (KO) mice showed an improved performance with a higher average speed (+25.2%, p=0.04) as well as enhanced running distances (+68.3%, p=0.03). This effect could be confirmed in forced running treadmill analyses. Analyses of fiber type composition of CS2-deficient skeletal muscles showed a dramatic switch towards slow-twitch fibers, with a predominant increase of IIa fibers in m. gastrocnemius (+56.2%, p=0.01) and type I fibers in m. soleus (+68.1%, p=0.007).

Reporter assays in myoblasts confirmed a dose-dependent inhibition of calcineurin by CS2. Consistently, *CS2* mutant mice revealed an excess of nuclear NFATc4 (+158.1%, p=0.017) as well as an increase in the expression of RCAN1-4 (4.0-fold, p=0.02), indicating enhanced calcineurin signaling *in vivo*. Taken together, CS2 modulates exercise performance *in vivo* via regulation of calcineurin/NFAT activity and subsequently the fiber type composition of skeletal muscle.

Dyxin/Lmcd1 mediates cardiac hypertrophy both *in vitro* and *in vivo*

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In order to identify new molecular mediators of cardiomyocyte hypertrophy, we performed a genome wide mRNA microarray screen of biomechanically stretched neonatal rat cardiomyocytes (NRCM). We found the novel sarcomeric LIM protein Dyxin/Lmcd1 being upregulated (5.6x, $p< 0.001$). Moreover, Dyxin was also significantly induced in several mouse models of myocardial hypertrophy including aortic banding and Ang-II stimulation, suggesting a potential role as a mediator of cardiac hypertrophy. To further test this hypothesis, we adenovirally overexpressed Dyxin in NRCM which potently induced cellular hypertrophy (150%, $p< 0.001$) and the hypertrophic gene program (ANF, BNP). Consistent with an induction of calcineurin signalling, the calcineurin-responsive gene Rcan1-4 was found significantly upregulated (3.2x, $p< 0.001$). Conversely, knockdown of Dyxin (-75% on protein level) via miRNA completely blunted the hypertrophic response to hypertrophic stimuli, including stretch and PE (both $p< 0.001$). Furthermore, PE-mediated activation of calcineurin signaling was completely blocked by knockdown of Dyxin as assessed by Rcan expression as well an NFAT-responsive luciferase construct.

To confirm these results in vivo, we generated transgenic mice with cardiac-restricted overexpression of Dyxin. Despite normal cardiac function (echocardiography), transgenic mice displayed significant cardiac hypertrophy in morphometrical analyses (3.9 vs. 3.5 mg/g LV/heart weight, $p< 0.05$). This finding was supplemented by a robust induction of the hypertrophic gene program including ANF (3.7-fold, $p=0.01$) and □-skeletal actin (2.8-fold, $p< 0.05$). Likewise, Rcan1-4 was found upregulated (+112%, $p< 0.05$). Taken together, we show that the novel sarcomeric z-disc protein Lmcd1/Dyxin is significantly upregulated in several models of cardiac hypertrophy and potently induces cardiomyocyte hypertrophy both in vitro and in vivo. Mechanistically, Lmcd1/Dyxin appears to signal through the calcineurin pathway.

An integrated functional genomics approach to systematically link drug activity in non-small cell lung cancer to genetic aberrations

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Tumors depending on activation of oncogenic signaling pathways encrypted by somatic genetic aberrations of the cancer genome have been causally linked with response to targeted therapeutics. However, no tools currently exist to systematically connect such aberrations to therapeutic outcome. We developed a systematic method to identify aberrations associated with therapeutically amenable oncogene dependency. First, we show by integrated genomic analyses that the genomes of a large panel of non-small cell lung cancer (NSCLC) cell lines are highly representative of primary NSCLC tumors in gene copy-number, oncogene-mutation and gene-expression space. Furthermore, we performed cell-based chemical perturbation experiments followed by complementary computational prediction analyses of activity and validated our approach phenotypically by recapitulating the unique clinical responsiveness of EGFR-mutant lung cancer to EGFR inhibition ($p < 0.0001$).

Applying comprehensive computational approaches integrating orthogonal genomic and biochemical datasets we identify predictors for clinically relevant compounds. We demonstrate that KRAS mutations confer enhanced Hsp90 dependency and validate this finding showing that HSP90 inhibition leads to significant tumor regression in KRAS-mutant lung tumors of lox-stop-loxKRASG12C transgenic mice. Next, we identify cells with amplification of EPH and SRC family genes with exquisitely sensitive to treatment with the src-abl inhibitor dasatinib ($p < 0.05$). Importantly, the activity of dasatinib in EPHA3-amplified lung tumors could also be confirmed in-vivo. Finally, the overall accuracy of our approach was further validated by stable knockdown of predicted drug targets and demonstration of suppression of tumor cell growth.

Thus, genomically annotated cell line collections may help translate cancer genomics information into clinical practice by defining critical pathway dependencies amenable to therapeutic inhibition.

PTEN loss in EGFR mutated non-small cell lung cancer activates EGFR and Akt, thereby contributing to an erlotinib-resistant phenotype

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EGFR inhibitors such as erlotinib or gefitinib induce tumor shrinkage in patients with adenocarcinomas harbouring mutations in the EGFR gene. Nevertheless, these tumors recur, in most cases due to the emergence of cells expressing the T790M resistance mutation of EGFR or amplification of the MET receptor tyrosine kinase gene. Mechanisms involving activation of downstream signalling transducers of EGFR contributing to upfront or acquired EGFR inhibitor resistance remain elusive. By applying unsupervised clustering of gene expression data on a large panel of genomically and phenotypically annotated NSCLC cell lines we identified an erlotinib-resistant and EGFR-mutant cell line lacking any known resistance mechanisms. By employing biochemical and cellular analyses we demonstrate that EGFR and downstream PI3-kinase signalling are uncoupled in these cells. We found homozygous loss of PTEN as a potential modulator of EGFR-dependency in these cells by computational analyses of differential genomic lesions. Remarkably, detailed gene knock-in and knockdown experiments not only implicated activation of Akt by PTEN loss but also revealed activation of EGFR, presumably by activation of Erk. Together, these mechanisms contributed to an erlotinib-resistant phenotype. These findings suggest a novel erlotinib resistance mechanism in EGFR-dependent tumors involving genomic loss of PTEN. Furthermore, our data supports the notion that integrative analyses of orthogonal datasets may identify oncogene dependencies in cancer cells.

High food intake and altered lipid metabolism are causes of obesity in the BFMI860 line

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The identification of candidate genes and natural genetic variations for obesity in mice facilitates the search for obesity-related genes in humans. As a novel model for polygenic obesity we use the high fatness-selected Berlin Fat Mouse Inbred 860 (BFMI860) line. In order to characterize energy intake and energy expenditure of BFMI860 mice, we analyzed food intake, assessed resting metabolic rate at thermoneutrality (RMRt) in relation to body composition and monitored the respiratory quotient (RQ) in BFMI860 and B6 control mice. High body fat accumulation in BFMI860 mice was mainly restricted to weeks 6-10 and was accompanied by hyperphagia, higher RQs and abnormally high blood triglyceride levels. Lean mass adjusted RMRt was not altered between lines. These results indicate, that in BFMI860 mice, the excessive body fat gain was associated with high energy intake and altered lipid metabolism. Assuming that BFMI860 mice and their obese phenotypes are of polygenic nature, this line is an excellent model for the study of obesity in humans, especially for juvenile obesity and hyperlipidemia.

Irradiation-enhanced mammalian target of rapamycin (mTOR)-targeted glioblastoma therapy with CCI-779 (temsirolimus)

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The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway plays a critical role in oncogenesis, and dysregulation of this pathway is particularly common in human malignant gliomas. In these tumors, activation of PI3K/Akt/mTOR signaling leads to cell cycle progression, neovascularization, escape from apoptosis and inhibition of autophagy, and is associated with poor prognosis. CCI-779 (temsirolimus), a soluble ester analogue of rapamycin, is a small-molecule inhibitor of the mTOR kinase that has been demonstrated to have some antiglioma activity. Given that postoperative radiochemotherapy is the standard of care in the first-line treatment of glioblastoma, this translational project aims to analyze whether CCI-779 improves the efficacy of irradiation in experimental glioma models *in vitro* and *in vivo*.

Hitherto, in six human malignant glioma cell lines, we observed that CCI-779 applied at effective but not yet immunosuppressive concentrations exerted marked antiproliferative, anticlonogenic and antiangiogenic activity that was enhanced when combined with irradiation. Moreover, CCI-779, when applied following radiosensibilization, inhibited invasiveness in a supra-additive way and reverted the known proinvasive effect of sole sublethal irradiation. These effects were independent of the *PTEN* status, and were paralleled by an unwanted feedback loop activation of Akt. Further *in vitro* experiments focus on autophagy, differential effects on glioma-initiating cells, and cRNA microarray analyses. In currently ongoing MRI-monitored, orthotopic glioma xenograft experiments, we assess whether a treatment approach of combined CCI-779 and irradiation would also result in antitumoral activity *in vivo.*

At this time, these results support the clinical evaluation of combined targeted mTOR inhibition with CCI-779 (Torisel™) and radiotherapy in patients with newly diagnosed glioblastomas.

Chondrocyte-like cells in vascular calcification originate from the bone marrow and not from the local vessel wall in LDL-receptor knockout mice

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Introduction: Recent studies report that vascular calcification is not a passive precipitation but a precisely regulated process, similar to embryonic osteogenesis. In this process chondrogenic metaplasia, performed by so-called chondrocyte-like cells, plays a decisive role. These cells have a morphological similarity to chondrocytes and ability to expremise cartilage typical proteins like collagen-II. The origin of these cells remains unknown. Possibilities are pericytes or VSMC from the local vessel wall or progenitor cells from the bone marrow. To get a distinct answer to this essentiell question of vascular calcification is the intension of this studie.

Material and Methods: Sublethally irradiated C57BL/6 LDLr-/- mice obtain bone marrow from ROSA-26 mice, which ubiquitously express the bacterial enzyme □-galactosidase. This enzyme marks bone marrow derived cells. To accelerate the creation of vascular calcification the mice were feed with a high-fat diet. Additionally aortic freeze-thaw injury of the infrarenal aorta abdominalis was performed to induce a physical injury of the vessel wall. 1, 3, 14 and 56 days after freeze-thaw injury, the aortic vessels were taken out, serially cutted and histological (Oil-Red O and calcein) and immunhistological (□-galactosidase/collagen-II double marking) methods were performed. Sections were analyzed by using confocal laser-scanning microscopy.

Results: 56 days after freeze-thaw injury all samples (n=7) show distinct intimal atherosclerotic calcification. 50,1 % (± 6,6 %) of cells within the calcified plaque are stained positive for collagen-II. 87,4 % (± 3,3 %) of these chondrocyte-like cells are simultaneously stained positive for □-galactosidase. Concordantly the chimera-analysis reveals a mean of 88,0 % (± 1,4 %) of ß-galactosidase positive/negative cells in blood specimens.

Conclusions: The experiments indicate that condrocyte-like cells originate from the bone marrow and infiltrate into the calcified plaque.

DJ-1 deficient mice show reduced numbers of VTA dopaminergic neurons and exhibit cognitive impairments

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Loss of function of DJ-1 (PARK7) is associated with autosomal recessive early-onset Parkinson´s disease (PD), one of the major age-related neurological diseases. In this study, we extended former studies on DJ-1 knock-out mice by analysing the dopaminergic system not only in young (2 to 6 months old), but also in old DJ-1 deficient mice (18 to 24 months old), generated using the gene trap technology. Although we did not detect any age-related dopaminergic neurodegeneration in the DJ-1 mutant mice, due to the large number of animals analysed, a highly significant reduction (about 10%) in number of dopaminergic neurons in the ventral midbrain throughout the entire lifespan became apparent. Specifically, within the ventral midbrain, DJ-1 deficiency led to a selective loss of dopaminergic neurons in the VTA but not in the SN. Furthermore, since DJ-1 has been implicated in mitochondrial function *in vitro* we analysed the effect of DJ-1 deficiency onto the mitochondrial respiratory chain *in vivo*. Interestingly, and for the first time we found already in young DJ-1 deficient animals, a compensatory up-regulation of mitochondrial respiratory complex activities. On the behavioural level, the DJ-1 deficient mice showed a slight impairment in locomotion. More notably, we detected a significant impairment in cognitive behaviour both in young and in old DJ-1 knock-out animals - which is known as a major non-motor and pre-clinical symptom of PD. Hence, behaviour phenotypes of the DJ-1 knock-out mice might be due to a dysfunction of the mesocorticolimbic VTA dopaminergic neurons known to be involved in modulation of cognition, motivation and reward. Furthermore, the DJ-1 deficient mice could also represent a valuable animal model to elucidate molecular mechanisms underlying early phases of PD.

A library of conditional mutations in mouse embryonic stem cells for the functional analysis of the mammalian genome (EUCOMM)

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The inactivation of all mouse genes will strongly advance biomedical research, similar in its impact to the sequencing of the human genome. In the framework of the German Gene Trap Consortium (GGTC), we have already established a library of mouse ES cells with gene trap mutations in more than 7,000 individual genes. Based on the success of this strategy, we have now extended our gene trap effort with an improved gene trap cassette that allows the generation of conditional alleles (the "Flex" system; Schnütgen et al., 2005, PNAS).

Conditional alleles are neutral mutations that can be activated in a time and tissue-specific manner by addition of Cre recombinase. Many human diseases occur in later age, and the conditional alleles will help researchers to look at diseases that have been difficult or impossible to model so far by conventional mutations.

The GGTC gene trap has been the basis for the European Conditional Mouse Mutagenesis (EUCOMM) project, which has been launched in 2006. The leading partners of the EUCOMM consortium are the Helmholtz Center Munich and the Sanger Center, UK. The EUCOMM project is coordinated with two other international consortia, the KOMP project in the USA, and NorCOMM in Canada. It is the common goal of these partners to generate conditional mutations for the entire mouse genome.

The specific objectives of EUCOMM are:

5,000 conditional gene trap mutations in mouse ES cells

8,000 conditional mutations by gene targeting in mouse ES cells

320 mouse mutant mouse lines for phenotypic analysis

20 Cre recombinase "driver" mouse lines EUCOMM mutant ES cells and vectors are being distributed by the EUCOMM distribution center at the Helmholtz Center Munich, and mice will be distributed by EMMA (www.emmanet.org) to provide cost-effective animal models to the scientific community. The list of availble EUCOMM resources can be found at the website www.eucomm.org.

Circulating tumor cells: quantification, molecular characterization and future prospects

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Disseminated tumor cells in the blood could be detected during an onward tumor development and allow for monitoring response to cancer treatment. Hence, there is a substantial interest in the development and optimization of techniques which identify such cells. The aim of our project is to quantify circulating tumor cells (CTCs) of breast cancer patients and to characterize them concerning their expression of ErbB- and Met receptors. In particular, we are interested in comparing patients with ErbB2 overexpression that are treated with chemotherapy and trastuzumab, and patients with low ErbB2 expression treated with chemotherapy only.

Techniques to identify CTCs can be broadly divided into cytometric and nucleic-acid-based approaches.

Cytometric approaches use immunocytochemical methods to profile individual tumor cells. An advantage of these techniques is that they allow further characterization of the cells at a molecular level, in terms of the expression of key biological markers, such as ErbB2 and EGFR. However, only small numbers of epithelial cells are found in the blood, even in patients with metastatic cancer (in general, < 10 cells/ml). Therefore, enrichment of the cells, e.g. by immunomagnetic methods is needed. An alternative strategy is the detection of tumor specific mRNAs as markers for CTCs by nucleic-acid-based techniques like qRT-PCR. As the stability of RNA in clinical samples, once released from cells, is poor, the detection of such transcripts in a blood sample is most probably associated with a viable tumor cell. This could be regarded as an advantage of the mRNA-based approach.

Successful and consistent tracking and quantification of CTCs in breast cancer patients would allow for identifying the potential for metastatic disease, managing risk stratification in the adjuvant setting and monitoring response to treatment.

From genetic findings to functional implications - experimental concepts for the comprehensive analysis of genetic variants

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Genome-wide association studies result in positional genetic findings that must be translated into the functional molecular and cellular effects of the identified variants. In order to generate an integrated mechanistic model, a detailed knowledge of the organisational structure of the gene, splicing patterns, transcriptional regulation and cellular function is indispensable. Depending on the precise position of trait-associated allelic variants within the genomic model, polymorphisms can influence either regulatory mechanisms (when located in promoter, intron or UTR regions), splicing events (exon/ intron boundaries, splice enhancer sites) or the resulting protein architecture and/or function (coding region). For each of the situations mentioned, different experimental approaches must be implemented to analyze the functional consequences of the allelic variants with respect to the observed phenotype. This presentation will give an overview of how genetic findings can be comprehensively followed up on a cellbiological / functional level depending on the type of genomic region affected. Based on exemplary data generated in our group, we will present functional read-out systems that are routinely applied to understand how genetic variants contribute to interesting traits like chronic inflammatory diseases and healthy aging. In particular, the examples will focus on experimental concepts that help to identify the functional implications of trait-associated genetic variants influencing transcriptional regulation (longevity gene *OLD1*), splicing pattern (sarcoidosis-associated gene *BTNL2*) and protein structure and function (Crohn disease-associated genes *CARD15*/NOD2 and *ATG16L1*).

Pathways & gene networks: Innate immunity and barrier function

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This project provides a translation of established disease genes into a molecular pathophysiology of inflammatory processes at epithelial interfaces. This concept relies on a systematic cell biology-based approach to accelerate the dissection of barrier disease susceptibility loci. The project will serve as a standardized, quality-controlled functional characterization approach of genes from systematic disease gene finding efforts to all groups in the consortium. The read-outs and functional assays will mainly address the disturbed barrier function and innate immune pathways. It aims at a quantitative integrated map of novel and known pathways, such as NOD-like receptors and autophagy.

The overall aims are:

- To understand quantitative biological effects of disease-associated sequence variants in a context of epithelial barrier function and innate immunity
- To systematically analyze the genotype-dependent gene expression profile by using the network´s unique tissue bank and a large typable lymphoblast collection (n>300)
- To describe the direct molecular framework, in which the proteins encoded by disease genes exert their cellular function
- Employ genome-wide siRNA studies to delineate the functional network of the genes and their crosstalk with other genes in pathways relevant for adaptive immune responses
- To unveil novel putative targets within these molecular frameworks developing new diagnostics, therapy and, ultimately, preventive strategies

Function of BACE1 and Neuregulins in the developing and adult nervous system

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BACE1 (beta-site APP cleaving enzyme), an aspartyl protease, plays a critical role in the production of amyloid Abeta peptides; insoluble plaques containing Abeta constitute the molecular basis of pathogenesis in Alzheimer's disease. We recently identified the principal physiological function of BACE1 to be the cleavage of Neuregulins, growth and differentiation EGF-like factors that are highly expressed in the peripheral and central nervous systems. Our previous work has shown that cleavage of Neuregulin-1 by BACE1 is required for signaling of axonally-expressed type III Neuregulin-1 to apposing Schwann cells during myelination. Interestingly Neuregulin-1 is a gene linked to schizophrenia and psychosis. We have now generated mice carrying compound mutations in BACE1 and specific isoforms of Neuregulin-1 with the aim of characterizing the functions of BACE1 in Neuregulin-1 signaling in the neonatal and adult mouse nervous system. These mouse models will also allow determination of possible side-effects due to inhibition of BACE1, which holds promise as a therapeutic approach in the treatment of Alzheimer's disease.

National Genome Research Network

Poster presentation abstracts

Symposium V

Genomic / Environmental Interaction

Association between variations in the *TLR4* gene and incident type 2 diabetes is modified by the ratio of total cholesterol to HDL-cholesterol

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Background: Toll-like receptor 4 (TLR4), the signaling receptor for lipopolysaccharides, is an important member of the innate immunity system. Since several studies have suggested that type 2 diabetes might be associated with changes in the innate immune response, we sought to investigate the association between genetic variants in the *TLR4* gene and incident type 2 diabetes.

Methods: A case-cohort study was conducted in initially healthy, middle-aged subjects from the MONICA/KORA Augsburg studies including 498 individuals with incident type 2 diabetes and 1,569 non-cases. Seven SNPs were systematically selected in the *TLR4* gene and haplotypes were reconstructed.

Results: The effect of *TLR4* SNPs on incident type 2 diabetes was modified by the ratio of total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C). In men, four out of seven *TLR4* variants showed significant interaction with TC/HDL-C after correction for multiple testing ($p < 0.01$). The influence of the minor alleles of those variants on the incidence of type 2 diabetes was observed particularly for male patients with high values of TC/HDL-C. Consistent with these findings, haplotype-based analyses also revealed that the effect of two haplotypes on incident type 2 diabetes was modified by TC/HDL-C in men ($p < 10^{-3}$). However, none of the investigated variants or haplotypes was associated with type 2 diabetes in main effect models without assessment of effect modifications.

Conclusions: We conclude that minor alleles of several *TLR4* variants, although not directly associated with type 2 diabetes might increase the risk for type 2 diabetes in subjects with high TC/HDL-C. Additionally, our results confirm previous studies reporting sex-related dissimilarities in the development of type 2 diabetes.

Air pollution and inflammtion: Gene-environment interactions in myocardial infarction survivors

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There is evidence suggesting that cardiovascular effects of air pollution are mediated by systemic inflammation which is regulated by genes involved in these pathways. We had earlier shown that the air pollution-fibrinogen response is modified by a promoter SNP of *FGB.*

We tested here a two stage approach. We apply a screening step for 136 SNPs located in 23 genes and 2 non-coding regions from inflammatory and detoxification pathways on the mean fibrinogen level and variability. We take statistically significant (adjusted for multiple comparisons) SNPs to the second stage of assessing the modification of the air pollution-fibrinogen response by these selected SNPs.

We conducted five independent panel studies with a standardized study protocol in a total of 895 myocardial infarction survivors from five European cities. Plasma fibrinogen levels and air pollution concentrations were determined repeatedly (N=5327). City-specific analyses were conducted using additive mixed models adjusting for patient characteristics, time trend and weather to assess the impact of air pollutants on plasma fibrinogen levels and its modification by genotype. City-specific estimates were pooled using meta-analysis methodology.

We identified *FGB* to be associated with increased fibrinogen level and 41 SNPs in 14 gene loci associated with increased variability in fibrinogen. Testing for gene-environment interactions, we found subjects homozygous in the minor allele of *TLR4* rs2770150 being associated with 35-fold stronger response than subjects homozygous in the mayor allele (p-value for interaction 0.0015). In conclusion, the two staged strategy identified in five independent study samples a new potential pathway of modulating the air pollution-fibrinogen response in myocardial infarction survivors.

Establishment of a psychophysical stress challenge in the German Mouse Clinic

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Chronic stress is a risk factor for the development of neurodegenerative diseases, whereas physical activity („exercise") can be protective (Kiraly & Kiraly, Int J Psychiatr Med 2005;35:75-89; Review). In this context, adult neurogenesis may play a role, since chronic, unpredictable and uncontrollable stress reduces adult neurogenesis (see Joels et al., Front Neuroendocrinol 2007;28:72-96 for review), and neurogenesis is reduced in neurodegenerative diseases like Parkinson's disease (Höglinger et al., Nat Neurosci 2004;7:726-35) and Alzheimer's disease (Waldau & Shetty, Cell Mol Life Sci 2008;May 26, Review).

To analyse the impact of stress on disease development in genetic mouse models of neurodegenerative and other diseases in the German Mouse Clinic, we currently establish a psychophysical stress challenge. To this end we aim to develop acute and chronic restraint stress protocols, that reliably induce prolonged behavioral changes (i.e. increased anxiety, passive coping or „learned helplessness") in mice of both sexes. First results in wildtype mice will be presented and discussed.

Olfactory function in genetic mouse models of Parkinson's disease

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Parkinson's disease (PD) is a progressive neurodegenerative movement disorder, which results mainly from a pronounced loss of dopaminergic neurons within the substantia nigra pars compacta as well as the presence of Lewy body pathology in the residual neurons. It is well established that olfactory deficits, whether measured by smell identification, recognition or sensitivity, are common in PD and evidence is accumulating that impaired olfaction occurs in the earliest stages of the disease and may precede the classical motor features by several years. The pathological background of olfactory deficits in PD is unknown. A possible explanation for the olfactory deficits in PD is related to impaired olfactory neurogenesis. The olfactory bulb is a region that receives new neurons throughout life. Diminished numbers of these cells have been documented in the subventricular zone in brains of PD cases (Muller et al., 2002). In mice dopamine depletion impairs precursor cell proliferation which leads to impaired fine olfactory discrimination (Enwere et al., 2004). The majority of PD cases appears to be sporadic, but several distinct loci, including autosomal dominant mutations in LRRK2 and autosomal recessive mutations in DJ-1 and PTEN-induced kinase 1 (PINK1), have been implicated in rare inherited forms that resemble idiopathic PD . Because genetic mouse models with these mutations showed in preliminary behaviour tests indications for olfactory deficits, we want to investigate their olfactory performance in detail. Therefore we established an olfactory test battery using a simultaneous smell discrimination task. After pretraining to associate a buried reward with an odorant that was designated [S+], mice had to chose by digging in the dish with [S+] scented shavings. First results will be presented.

Classification of phenotype-to-genotype relationships for neurodegenerative diseases

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The phenotypic diversity of neurodegenerative diseases, such as Parkinson's disease (PD), spinocerebellar ataxias (SCAs), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD), may help to identify new disease genes or gene interactions. In this project, we aim to standardize the wealth of clinical information available on PD, AD, HD, ALS and SCAs, and weight the frequencies/relevance of various symptoms in order to define syndrome families. Phenotype similarity scores will be obtained in a validated, automated approach. At the same time, a lymphoblastoid cell line repository for patients with neurodegenerative diseases will be established. Combining the clinical information with the genetic and biochemical data obtained in the other subprojects of the NeuroNet, phenotype-interaction networks can be established to predict associations of genes to diseases, protein-protein interactions (PPI) to diseases and drugs to diseases.

The concept of endophenotypes in psychiatric diseases

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Although the prominent role of genetics in psychiatric diseases has been established in various family, twin and adoption studies over the last decades, the identification of concrete contributing genes has been demanding. The reasons for this are manifold, including inconsistencies in psychiatric classification systems, complexity and heterogeneity of psychiatric disorders, epistatic effects and intervening environmental factors. In recent years interest has focused increasingly on the concept of endophenotypes. Genetic analyses have concentrated on discrete phenotypes supposedly linked to a particular psychiatric disorder by common neurobiological pathways, instead of studying the complex disease itself. Several endophenotypes have been established for psychiatric diseases including electrophysiological abnormalities and alterations in structural and functional brain imaging. Although results seem to be getting more consistent and reliable, several concerns have also emerged with the experience gained on the topic. This talk will give an overview of the prospects and limitations related to endophenotypes in psychiatric diseases. Also essential prerequisites for successful endophenotypes in the future as well as applications for psychiatric diseases employing dynamic models of a patients' individual pathophysiology in terms of systems neurobiology will be presented.

National Genome Research Network

Poster presentation abstracts

Symposium VI

Transfer from Genomics to Application

Characterization and functional analysis of Poloxin: a small molecule inhibitor targeting the polo-box binding domain of Polo-like kinase 1

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Polo-like kinase 1 is overexpressed in a variety of human tumors and its expression correlates with aggressive proliferation of tumor cells and prognosis of tumor patients. Plk1 has been established as a promising target for antitumor therapy. Indeed, several small molecule inhibitors, targeting the enzymatic domain of Plk1, have been identified. The unspecificities associated with ATP-competitive kinase inhibitors prompted us to explore an alternative strategy to inhibit Plk1. The unique polo-box binding domain (PBD) of Plk1 has been taken for the screening of small molecules, based on a high-throughput fluorescence polarization assay. The natural product Thymoquinone (TQ) and its derivative Poloxin have been identified as the first known inhibitors of the Plk1 PBD. Poloxin and TQ inhibit the function of Plk1 PBD *in vitro* and reduced the binding capability of the PBD with endogenous phosphorylated Cdc25C, which is one of the best characterized interaction partners of Plk1. Moreover, Poloxin and TQ cause Plk1 mislocalization, chromosome congression defects and mitotic arrest in tumor cells. Poloxin and TQ inhibit proliferation and induce apoptosis in various tumor cells. Interestingly, Poloxin sensitizes tumor cells towards chemotherapeutic agents, such as cisplatin. Further evaluation of Poloxin *in vivo* is in progress.

Classification and identification of bacteria by mass spectrometry and bioinformatic tools

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The definite determination of bacterial species is a laborious process that requires extensive manual labour. New efficient methods for bacterial detection can therefore help clinicians and microbiologists in minimising their efforts in diagnostics.

We present a standardized method for automated bacterial analysis that is based on MALDI mass spectrometry detection of patterns of protein masses from whole bacterial cells. We applied this method for classifying and identifying a number of different bacteria. To support users with data analysis tools, we generated a bacterial mass spectra database and tested suitable software packages that are demonstrated herein.

References: Sauer S, Freiwald A, Maier T, Kube M, Reinhardt R, Kostrzewa M, Geider K. Classification and identification of bacteria by mass spectrometry and computational analysis. PLoS ONE. 2008 Jul 30;3(7):e2843.

PaCaNet: A translational genome research network in pancreatic cancer

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Virtually every pancreatic cancer patient will die within the first year after diagnosis, making pancreatic cancer the 4th to 5th most common cause of cancer related deaths in the western world. Conventional means of diagnosis and treatment are unsatisfactory at present. The genome project has generated knowledge and technology with great potential to contribute to the understanding of the molecular pathogenesis in the pancreas and to provide molecular targets. However, even though multiple genome scale screening approaches of pancreatic tumors and their preneoplastic lesions have been conducted, only few targets have reached the level of preclinical or clinical applications. The fact that the tumor is hard to study in humans due to its particular anatomical and histopathological characteristics, the lack of well characterized clinical resources, and in particular the limited availability of valid *in-vitro* and mouse models of the disease have been rate limiting steps so far. The PaCaNet consortium is an Integrated Genome Research Network comprising groups who

i) set the standards of clinical care and histopathology of pancreatic cancer and its precursor lesions,

ii) have pioneered the use of high-throughput genome technology in pancreatic research,

iii) have generated *in-vitro* and *in-vivo* models of the disease and

iv) were among the first to transfer individual target genes or groups of target genes into preclinical and clinical applications.

In the PaCaNet project, these German centers of excellence in pancreatic cancer research are now joined by genome research groups and partners from the pharmaceutical industry in an integrated approach for an efficient characterization and exploitation of genome project candidate genes for pancreatic cancer. The prime objective is to foster the rapid development and transfer of novel genome-based, molecular targeted therapeutic and diagnostic approaches from basic research, over preclinical testing into clinical applications.

Targeted next-generation-sequencing by specific capture of multiple genomic loci using low-volume microfluidic DNA-arrays

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Genome-wide DNA polymorphism analyses greatly benefit from the introduction of a new generation of ultrafast sequencing technologies. These so-called next-generation-sequencing (NGS) platforms have massively increased the throughput of sequence data and decreased cost and effort for sequencing projects. Nevertheless, all NGS platforms are unable to specifically target desired DNA sequences what limits the prediction of genetic variation in regions of interest. We used microfluidic DNA-arrays with a customized set of capture probes to specifically enrich multiple discontiguous genomic sequences out of complex human DNA libraries. In combination with an integrated hardware the process of enrichment was highly automated leading to DNA samples that were directly used for sequencing on an Illumina/Solexa Genome Analyzer II. The analysis of the sequencing data reflects the over 500-fold enrichment of the targeted sequences resulting in an adequate coverage for reliable prediction of genetic variations. For the data presented here we designed arrays with capture probes to focus on exon sequences of more than 100 cancer-related genes. This microarray matrix is used for DNA enrichment and the subsequent detection of disease-related SNPs in human specimen samples.

Indexed paired-end next-generation sequencing for medical resequencing demonstrated in patients with congenital hyperinsulinism (CHI)

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CHI is characterized by severe hypoglycemia due to excessive insulin secretion from pancreatic ß-cells. Two histologically and genetically distinct groups are recognized among patients with CHI. (I) The diffuse form involves the entire pancreas and is predominantly caused by autosomal recessive inheritance with mutations in several genes, mainly ABCC8 and KCNJ11; (ii) The focal form shows localized adenomatosis of islet cells and is caused by ABCC8 or KCNJ11 germline mutations of the paternal allele and a somatic loss of the maternal allele.

Capillary sequencing of the coding region results in a low mutation detection rate: Out of 44 patients with diffuse CHI, 12 were homozyous or compound heterozygous for ABCC8 mutations, 9 were heterozygous and in 23 cases no mutations were found. In order to detect further rare variants, we resequenced the entire genomic region of the ABCC8 and KCNJ11 genes (100 kb) on a GA II system in 24 samples and evaluated the sensitivity and specifity of variant detection. The region was amplified with 19 long-range PCR reactions. For library construction, a ß-version of the Illumina indexed paired-end kit was used and up to 12 samples were processed in a single lane. Data were analyzed with the MAQ software. Coverage was between 300- and 5000-fold. Preliminary analysis of 12 samples revealed several false positive variants that were only found on either the forward or reverse strand and showed preference for specific neighboring nucleotides. After filtering for this systematic error, we detected all 21 previously sequenced coding SNPs/mutations and indels. We did not detect false positives in the coding region. Aside from known variants, we detected further 44 unknown SNPs and 4 unknown indels in the intron- and intergenic regions. Population frequencies of these variants are being investigated. In summary next-generation sequencing with indexing promises accurate and efficient mutation detection for defined genomic regions.

Subgenome fractionation for high throughput sequence analysis

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We apply two approaches to enrich DNA regions of interest: First, we use the method of microarray-based genomic selection (MGS) for enriching genes involved in cardiomyopathies and arrythmias. We selected the exons of 2000 genes (ca. 1 Mb) on oligo microarrays to enrich the DNA of patients with cardiomyopathies and arrythmias and healthy people. By this method we achieved average enrichment factors of 120 to 900. We are planning to further optimize this procedure in order to apply multiple samples at a time using multiplex identifier (MID) to be able to enrich the DNA of several patients on the same microarray. This will also enable us to detect whole exon or gene deletions in individual patients. The enriched DNA is ready for downstream high throughput sequencing by Roche/454 pyrosequencing technology.

Moreover it is planned to analyze promoter regions of disease genes related to brain tumors in close collaboration with the Brain Tumor Network (BTN in NGFN-Plus), using samples of up to 50 patients. Bisulfite sequencing should than be able to detect differences in diseased and normal tissue, by using only minute amounts of DNA for sequencing .

Our second approach aims to enrich smaller regions by biotinylated oligonucleotides. By this method we obtained enrichment factors of more than 300. Initially, our primary application will be the identification of integration sites of gene therapy vectors within the genome of targeted cells in gene therapy approaches.

We are most interested to make use of our developments in other NGFN projects to extent the methodology to a wider range of applications.

Pathway enrichment and next generation re-sequencing of 68 *E. coli* genes using HybSelect™

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We have selected 68 genes from *Escherichia coli* K-12 MG1655 from three major pathways for next generation re-sequencing. We have generated five complete datasets for analysis of our new sequence selection method HybSelect™.
HybSelect uses febit´s extremely flexible microarrays and Geniom RT Analyzer to analyze any genomic region of interest. The microfluidic design of the biochip allows highly efficient small-volume hybridization, washing and elution of captured sequences. In addition, the fully automated Geniom RT Analyzer performs HybSelect with very little hands-on time. After recovery from the biochip, the captured DNA can easily be analyzed on a Illumina GA II or any other next generation sequencer.

With an optimized protocol, we were able to obtain up to 874fold median coverage of the 68 targeted *E. coli* genes (89,344bp). We have used the *E. coli* enrichment experiments to study basic performance parameters like reproducibility, error rates or multiplexing capacity in order to demonstrate the power and accuracy of the method.

Subgenome fractionation for high troughput sequencing

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The recent advent of next generation sequencing (NGS) platforms has massively decreased cost and effort for sequencing projects and holds promise to transform genetic variation studies to a much more systematic and comprehensive field. However, these technologies are still far from being applicable to whole genome resequencing of complex, eukaryotic organisms due to limited data output. In many cases, it would be desirable to focus on individual genomic subsets of interest by reducing the sequence complexity of the sample.

Within the NGFN-transfer project "Subgenome Fractionation for High Troughput Sequencing " a consortium from industry, academia and the clinical setting is set out to develop a robust method for enrichment of subgenome fragments for NGS.

We employ a flexible method to selectively capture sequence fragments out of complex, eukaryotic genome libraries for NGS, based on hybridization to DNA-microarrays. Using microfluidic array architecture and an integrated hardware approach, the processing of samples will be highly automated and require minimal hands-on-time.

Furthermore, the workplan includes the evaluation of the enrichment technology concerning disease-relevant genome-regions and the development of dedicated "ready-to-use" analytical selection matrices. Intended applications are re-sequencing of coding sequence, promotor regions, CpG islands and candidate regions established by association and linkage studies. The technology will be made applicable to detect germline mutations (in patients with inherited diseases) as well as somatic sequence alterations (in neoplasia) and will be optimized to work with genomic DNA (searching for point mutations, insertions, deletions, and epimutations) and cDNA (searching for non-synonymous mutations, frame shifts, and alternative splice forms).

We will present the outline and goals of the project and will report first results on enrichment of genomic regions of the human genome in the megabase range.

Development and validation of new diagnostic, preventive and therapeutic tools for the prevention of cardiovascular diseases and disorders (CVD) in chronic kidney disease (CKD)

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The consortium applies the novel tools "proteomics, peptidomics and metabonomics, and genotyping", which allow assessing the complete transcription and translation of the genomic capital to elucidate the genetic and physiological background of CVD in CKD patients. This approach is focused on human samples i.e. tissues, cells and body fluids as humoral targets are altered in CVD of CKD patients. NT**CVD** applies "forward genetics" from phenotype to gene to remedy the causes of the enormously accelerated cardiovascular morbidity and death in CKD (stage 3-5) and to develop novel diagnostics and therapeutics, based on molecular genotyping and phenotyping. This will be done (A) by elucidating the role of recently identified mediators relating to CVD in CKD by using bioassay approaches and pattern analysis of CKD patient samples, and (B) by the identification of yet unknown mediators. Findings and results will be translated directly into new diagnostic and therapeutic devices for the prevention and treatment of CVD in CKD by collaborative efforts of the industry partners (one SME, one industrial company) within NT**CVD**.

Cell-specific decoy oligodeoxynucleotide delivery to the failing heart

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Heart failure has a high unmet need for more effective and innovative medications that may be causally linked to the complex interaction of mutations in various susceptibility genes which is likely to underlie this disease. An aberrant transcriptional control of the expression of disease-related gene products may be readily alleviated by administering a decoy oligodeoxynucleotide (ODN) directed against the misguided transcription factor. Despite the great advantages of these nucleic acid-based drugs in terms of topical administration, delivery to cardiac fibroblasts or myocytes marks a serious challenge.

Thus, the specific aim of this project is to develop approaches to deliver decoy ODNs preferentially into cardiac myocytes and fibroblasts when administered intravenously. Even though these short double-stranded DNA molecules in contrast to single-stranded DNA antisense or double-stranded siRNAs readily enter cells when brought into close proximity to them, in patients with heart failure the cardiac compartment can only be efficiently reached via a transvascular approach. This delivery mode however is limited by the vascular wall, which acts as a diffusion barrier for the decoy ODNs. To overcome this deficit, we are developing strategies to load decoy ODNs on empty Adeno-associated virus (AAV) vectors. An efficient cardiac transfer shall be achieved by using adeno-associated virus vectors known for their strong cardiac tropism such as AAV-9 or targeted vectors isolated from an AAV peptide display library. Alternatively, the decoy ODNs shall be loaded on microbubbles which can be specifically destroyed by the aid of an ultrasound transducer probe in the capillaries of the heart resulting in microjets which increase vascular permeability.

Protein analysis of formalin-fixed breast cancer tissues for diagnosis, prognosis, and therapy guidance

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The challenge of translating proteomic profiling to the bedside is to apply technologies for the analysis of tumour tissues routinely obtained at biopsy or surgery without substantially modifying the clinical workflow. Clinical tissues are typically formalin-fixed and paraffin-embedded (FFPE) for histopathological diagnosis, preventing their routine use for multiplex or high-resolution proteomic technologies, e.g. protein lysate microarrays or 2D-gel electrophoresis. In order to shift diagnosis to prediction, novel tools are needed for precise protein measurements of clinical tissues. We have developed technologies for tissue proteomics to elucidate protein expression quantitatively in FFPE samples. The main goals of this consortium are: (a) precise measurements of disease markers in routine FFPE samples to assist in therapy decisions for breast cancer patients; (b) extension of our technology for the identification and characterization of novel protein markers for response prediction and prognosis. Specifically, we will use our technology (1) to determine urokinase-type plasminogen activator (uPA) and its inhibitor, PAI-1, as predictive markers for node-negative breast cancers in FFPE samples; (2) to measure tyrosine kinase-dependent signalling pathways for antibody-based therapy; (3) to establish new markers for response prediction using differential 2D-gel electrophoresis and mass spectrometry. Our novel proteomics tools have the potential to become standard techniques in molecular pathology for analysing FFPE tissues to improve patient outcome.

Whole genome and transcriptome amplification in large biobanks

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Biobanks are a key resource in unravelling the molecular basis of diseases, identification of new targets for therapy and improvement of attribution in drug discovery and development. The scientific trend in biobanking shows the need for stable techniques for amplification of biomaterials, which can be used for samples stored under very different conditions. The focus of the project is the standardisation and validation of the innovative techniques of whole genome amplification (WGA) and whole transcriptome amplification (WTA) in the context of biobanks. A general standardized protocol for WGA and WTA procedures that use Phi29-DNA-polymerase in biobanking will be developed.The major aims of our project are:

1. To establish standardized WGA protocols for large biobanks

2. To develop standardized WGA tools to recover genomic DNA, which is in plasma or serum samples and from FFPE- tissue or blood spots

3. To optimize the WGA procedure by extensive quality control measures of WGA products

4. To develop and establish WTA of large biobank samples

5. To optimize WTA procedures by extensive quality control of WTA products

Furthermore, the concept of the project is to transfer the results of WGA and WTA solution to national and international organisations in the field of biobanking. The development of the proposed, innovative and specialized tools and customized solutions will help to expand and secure biobanks.

Activation of BMP4 signalling via inhibition of HDAC11 represses neuroblastoma tumorigenicity

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Highly resistant relapses remain a major challenge in neuroblastoma (NB) therapy. Here, we identify a novel mechanism suppressing NB cell tumorigenicity. Using whole genome expression analysis, this study identified bone morphogenetic protein 4 (*BMP4*) as the strongest immediate early histone deacetylase inhibitor (HDACI)-response gene. Chromatin immunoprecipitation revealed that HDACIs induce an accumulation of acetylated histone H4 associated with the *BMP4* promoter. siRNA-mediated knockdown of the 11 HDACs belonging to classes I, II and IV showed that only knockdown of HDAC11 mediates the induction of *BMP4*. HDAC11 overexpression reduced endogenous *BMP4* levels. The BMP-antagonists gremlin and noggin blocked the differentiating effects induced by HDAC11 knockdown. Recombinant human BMP4 (rhBMP4) activated the Smad signalling cascade and decreased both proliferation and colony formation in vitro. In vivo administration of rhBMP4 strongly reduced both NB formation and growth in nude mice.

In conclusion, activation of BMP4 signalling via inhibition of HDAC11 represses NB cell tumorigenicity both in vitro and in vivo. The data highlight both HDAC11 as relevant target for HDACI-mediated therapeutic intervention and the administration of rhBMP4 as novel strategy against advanced NB.

Histone deacetylase 8 in neuroblastoma tumorigenesis

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Purpose: The effects of pan-histone deacetylase (HDAC) inhibitors on cancer cells have shown that HDACs are involved in fundamental tumor biological processes such as cell cycle control, differentiation and apoptosis. However, due to the unselective nature of these compounds, little is known about the contribution of individual HDAC family members to tumorigenesis and progression. The purpose of this study was to evaluate the role of individual HDACs in neuroblastoma tumorigenesis.

Experimental Design: We have investigated the mRNA expression of all HDAC1-11 family members in a large cohort of primary neuroblastoma samples covering the full spectrum of the disease. HDACs associated with disease stage and survival, were subsequently functionally evaluated in cell culture models.

Results: Only HDAC8 expression was significantly correlated with advanced disease and metastasis, and downregulated in stage 4S neuroblastoma associated with spontaneous regression. High HDAC8 expression was associated with poor prognostic markers, poor overall and event-free survival. Knockdown of HDAC8 resulted in inhibition of proliferation, in reduced clonogenic growth, cell cycle arrest and differentiation in cultured neuroblastoma cells. Treatment of neuroblastoma cell lines as well as short term culture neuroblastoma cells with a HDAC8 selective small molecule inhibitor inhibited cell proliferation, clone formation and induced differentiation, and thus reproduced the HDAC8 knockdown phenotype. Global histone 4 acetylation was not affected by HDAC8 knockdown or by selective inhibitor treatment.

Conclusion: Our data point toward an important role of HDAC8 in neuroblastoma pathogenesis and identifies this HDAC family member as a specific drug target for differentiation therapy of neuroblastoma.

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Revealing novel associations between glycosoaminoglycan degradation and Met signalling in cancer

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Mortality of cancer is highly associated with metastasis. The formation of metastases requires cancer cell detachment from their primary tumour. In order to investigate the early events of cell dissociation, we performed a whole human genome siRNA screen using a library of 21,167 siRNAs. The results of this assay revealed both characterized and uncharacterized proteins according to PubMed based Ingenuity analysis. As we were highly interested in the integration of the non-characterized proteins into known functional networks, we developed a method which allows a classification in KEGG pathways based on InterPro domains. Using this method, we found that the KEGG pathway for glycosaminoglycan (GAG) degradation to be overrepresented in our candidate list. In total, we found 31 proteins which belong to the glycosaminoglycan degradation pathway. Given GAGs are the integral part of the extracellular matrix and cell surface proteins, we hypothesized that misregulation of GAG degrading proteins aid in promoting metastasis by modulating the interactions between tumour cells and their microenvironment. We functionally validated the role of candidates in metastasis events using a wound healing screen and found that downregulation of 14 out of 31 candidate proteins either activated or impaired epithelial cell migration. Since GAGs are able to form ligand-receptor complexes and Hepatocyte growth factor and its receptor, the tyrosine kinase Met, play a key role in the progression of metastasis in a variety of cancers, next we examined if Met signalling is affected once the proteins involved in cell migration are downregulated. Our results strongly suggest that hyal2 siRNA impairs HGF induced Met activation and downstream signalling in cancer cells. We conclude that Hyal2 inhibitors could serve as potential drugs in Met induced metastases formation.

Keywords: Metastasis; Cell detachment; InterPro-IDs; Glycosoaminoglycan degradation; Cell migration, Met signalling

Metabolic profiling reveals distinct variations linked to nicotine consumption in humans - first results from the KORA study

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Exposition to nicotine during smoking causes a multitude of metabolic changes that are poorly understood. We quantified and analyzed 198 metabolites in 283 serum samples from the human cohort KORA (Cooperative Health Research in the Region of Augsburg). Multivariate analysis of metabolic profiles revealed that the group of smokers could be clearly differentiated from the groups of former smokers and non-smokers. Moreover, 23 lipid metabolites were identified as nicotine-dependent biomarkers. The levels of these biomarkers are all up-regulated in smokers compared to those in former and non-smokers, except for three acyl-alkyl-phosphatidylcholines (e.g. plasmalogens). Consistently significant results were further found for the ratios of plasmalogens to diacyl-phosphatidylcolines, which are regulated by the enzyme alkylglycerone phosphate synthase (alkyl-DHAP) in both ether lipid and glycerophospholipid pathways. Notably, our metabolite profiles are consistent with the strong down-regulation of the gene for alkyl-DHAP (*AGPS*) in smokers that has been found in a study analysing gene expression in human lung tissues. Our data suggest that smoking is associated with plasmalogen-deficiency disorders, caused by reduced or lack of activity of the peroxisomal enzyme alkyl-DHAP. Our finding provides new insight into the pathophysiology of smoking addiction. Activation of the enzyme alkyl-DHAP by small molecules may provide novel routes for therapy.

Molecular correlates of age-dependent seizures in a neonatal-infantile epilepsy

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Benign familial neonatal-infantile seizures (BFNIS) is an autosomal dominant epilepsy syndrome characterized by afebrile partial or secondarily generalized seizures occurring transiently in the first weeks and months of life. We identified 3 novel mutations in the brain sodium channel Nav1.2 (gene: SCN2A) in 3 patients with typical infantile seizures, one of whom also suffered from episodes of ataxia lateron. To characterize the functional defects of these mutations, they were introduced into the human the Nav1.2 channel in both the neonatal and adult splice variants, respectively, expressed in the mammalian cell line tsA201 together with their auxiliary beta1 and beta2 subunits, and functionally studied using the whole cell patch clamp technique. Compared with wild type (WT) channels, the mutant channels showed increased persistent sodium current, a slowing of fast inactivation, acceleration of recovery from fast inactivation, or shifts in the voltage-dependence of activation and inactivation. All these gain-of-function changes may well trigger a neuronal hyperexcitability and epileptic seizures. Since these effects were observed in both neonatal and adult splice variants, this cannot explain the age dependence of seizure occurrence. To unravel the transient nature of this epileptic syndrome, we studied the differential developmental expression of this channel and another sodium channel (Nav1.6) by using specific antibodies in mouse brain slices. Both channels are highly expressed at axon initial segments (AIS) of principal neurons throughout the brain, but they are differentially developmentally regulated: whereas Nav1.2 is transiently expressed in early stages of development (P5-15), Nav1.6 is not expressed at all early on but the main channel in adult animals at the AIS (increasing expression from P15 on). This finding can perfectly explain the transient nature of BFNIS providing the first molecular explanation for an age-dependent epilepsy.

Identification of potent and selective PI3Kg inhibitors using Kinobeads™ proteomics

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The Kinobeads™ platform developed at Cellzome enables the screening of compounds against kinases in their physiological setting directly from cell or tissue lysates. Combined with quantitative mass spectrometry, more than 100 kinases can be assayed in a single experiment, including some that are difficult to access by conventional biochemical assays. We described here the PI3Kg project where we applied the Kinobeads™ technology from the initial library screen of ~10,000 compounds as primary assay to lead optimization and for profiling the selectivity of key leads. Several of the leads show good drug-like properties and efficacy in relevant animal models.

iCHIP- central translational database for the brain tumor network

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Our integration center iCHIP serves as the central data backbone platform for the IG BTN^{plus} consortium in NGFN^{plus}. Currently, the brain tumor data collection within iCHIP from NGFN2 comprises the arrayCGH study (B. Radlwimmer), the microarray dye swap study (M. Hahn) as well as the p53 and the methylation status measurements. These studies and measurements are based on the core glioma collection with about 140 tumor samples. The existing and established brain tumor NGFN2 database will be adapted in order to integrate further new studies that will be performed in the time course of NGFNplus. As a crucial issue in the area of translational research, the link between clinical and molecular biological studies will be addressed. In spite of current progresses in genome annotation, it is still not trivial to map genes, transcripts and proteins to each other in a unique way. iCHIP will integrate new molecular data types by providing links and automatic mechanisms between genes, transcripts, proteins and transcriptional regulators.
Statistical correlations with histological and clinical data of the NGFN glioma core collection documented in the iCHIP-database will be used to assess the diagnostic and prognostic value of experiment measurements.

iCHIP is an advanced and comprehensive database system, designed in general to facilitate intelligent queries across several experimental data types. By correlating clinical data and experimental measurements in genewise and genome wide comparison, iCHIP now represents an adept platform for data integration and analysis in the emerging translational research field.

National Genome Research Network

Company Satellite Lunch Sessions
Oral presentation abstracts

Roche Diagnostics GmbH

xCELLigence RTCA:
Greater Insight, True Understanding
Moving Cell-Based Assays from Art to Science

Bill Cigich, Consultant for Roche Applied Science, Mannheim

The new xCELLigence System from Roche Applied Science is a microelectronic biosensor system for cell-based assays, providing dynamic, real-time, label free cellular analysis for a variety of applications in drug development, toxicology, cancer research, and medical microbiology and virology. The xCELLigence system provides the real time monitoring of adherent cells, which allows for monitoring of response kinetics over virtually any time frame, providing greater insight into dynamic responses to compounds which affect growth and morphology. In addition, because the cells are monitored from plating until the end of the assay, xCELLigence allows the quantification of cellular status prior to compound addition, resulting in a high degree of quality control and reproducibility from assay to assay. The basis of the technology and cytotoxicity and GPCR applications will be discussed.

Roche Diagnostics GmbH

The Genome Sequencer FLX System from Roche

Long reads – Get the complete picture and avoid high downstream costs

Dr. Marcus Droege, MBA, Roche Applied Science, Marketing Director Genome Sequencing

The Genome Sequencer FLX System (GS FLX), powered by 454 Sequencing, is a next-generation DNA sequencing technology featuring a unique mix of long reads, exceptional accuracy, and ultra-high throughput. It has been proven to be the most versatile of all currently available next-generation sequencing technologies, supporting many high profile studies in over 7 applications categories. GS FLX users have pursued innovative research in de novo sequencing, re-sequencing of whole genomes and target DNA regions, metagenomics, and RNA analysis. 454 Sequencing is a powerful tool for human genetics research, having recently re-sequenced the genome of an individual human, currently re-sequencing the complete human exome and targeted genomic regions using the NimbleGen sequence capture process, and detected low frequency somatic mutations linked to cancer.

This presentation will provide a short overview about the 454 Sequencing technology, and will focus on applications possible to address with the Genome Sequencer FLX system, with special emphasis on human re-sequencing. It will also provide information on the newest product developments, including the 2008 launch of kits allowing to generate more than 5 gigabases per week at an average read length of >400 bases on the today's FLX instrument.

Applied Biosystems GmbH

Ultra High Throughput sequencing analysis of Transcriptome in single cells with SOLiD 3 System .

Raimo Tanzi, Director Business Development, Applied Biosystems Europe

The analysis of transcriptome by Next Generation Sequencing (RNA-Seq) is rapidly becoming the natural substitute for microarray analysis of gene expression in functional biology. The main benefits of SOLiD technology for this application are the very high number of tags generated (more than 150 million on a single slide, 300 in a full run) which allows very deep analysis of expression and the unbiased approach, which allows to overcome the limitations of microarray approach.
We developed a sequencing-based gene expression profiling assay at single cell resolution by combining a modified single cell whole transcriptome amplification method with the next generation sequencing technique, the SOLiD™ System. Using this assay, we showed that blastomeres in a four-cell stage embryo have similar gene expression, which is compatible with the fact that they have similar developmental potential. We proved that, compared to cDNA microarray technique, our single cell cDNA SOLID sequencing assay can detect expression of thousands of more genes. Moreover, for the genes detected by both microarray and SOLID sequencing, our assay detected new transcript variants for a large proportion of them, which unambiguously confirms at single cell resolution that the transcriptome complexity is higher than traditionally expected.
By analyzing the transcriptome at spectacular and unprecedented depth and accuracy, thousands of new transcript variants/isoforms were unambiguously found expressed in mammalian tissues or organs. These advances greatly accelerate our understanding of the complexity of gene expression regulation and networks for mammalian cells. The technique usually needs mg amounts of total RNA for analysis, which corresponds to hundreds of thousands of cells. However, under certain conditions, it is practically not possible to get such amounts of materials for analysis
Here we modified a single cell whole transcriptome amplification method to make it permissive to amplify cDNAs as long as 3kb in an efficient and unbiased manner (8,9). We combined this modified single cell cDNA amplification method with Applied Biosystems' next generation sequencing (NGS) technology, the SOLiD™ System, to set up a single cell whole transcriptome assay.

With this novel approach, it is feasible to get gene expression profiles at single cell resolution, which enables us to ask fundamental biological questions previously not possible, especially in the field of early embryonic development, and to understand biology at the single cell resolution, which is the uniform functional unit of any organism.

The LightCycler® 480 System – Rapid by Nature, Accurate by Design
Ongoing Technological (R)evolution

Dr. Andreas Hein, Roche Diagnostics GmbH, Sales and Marketing Roche Applied Science

With introduction of the LightCycler® PCR system 10 years ago, Roche Applied Science has set a new standard in real-time PCR. LightCycler® instruments are well known for their sensitivity, accuracy, speed and flexibility. Following the same lines, the LightCycler® 480 system offers the highly innovative technology of LightCycler® systems for multi-well based assays. For the first time in a PCR instrument, the LightCycler® 480 system incorporates Therma®Base technology for optimal heat transfer and distribution to all sample positions resulting in unparalleled well-to-well temperature homogeneity and excellent inter-well, inter-cycle reproducibility. In combination with a CCD camera and a patented optical system, uniform collection of signals across the plate is attained. Additionally, the LightCycler® 480 system can be integrated into a fully automated workflow via a LIMS/Bar-Code Module. Offering 5 excitation and 6 detection filters that can be flexibly combined the LightCycler® 480 system is compatible with any standard assay format and application, e.g. gene expression and mutational analyses. Besides, high quality of the LightCycler® 480 design enables advanced applications such as High Resolution Melting. This exciting new approach, also called "Gene Scanning", can be applied for such analyses as detecting SNPs, insertions, deletions, DNA methylation patterns or screening of amplicons for unknown mutations. Gene Scanning therefore can be used as alternative or in addition to sequencing making the LightCycler® 480 system the most flexible currently available real-time PCR system.

TMF e.V.

TMF - Contact partner and common platform for networked medical research

Dr. Arne Pfeufer, Spokesperson of the Molecular Medicine Working Group, Competence Network Atrial Fibrillation / Helmholtz Centre Munic - German Research Centre for Health and Environment (GmbH)

An efficient, high-quality infrastructure is a major precondition for cutting-edge research. The principal aim of the TMF (Telematikplattform für Medizinische Forschungsnetze e.V.) is therefore to improve the organization and infrastructure for networked medical research, i.e. clinical, epidemiological and translational research.

The joint activities not only focus on legal and ethical frameworks for networked medical research but also on the development of IT infrastructure, quality management activities for science-initiated trials and questions on the intermeshing of research and patient care. As a result, expert opinions, studies, concepts, requirements specifications, services and tools are available to the research community.

The number and range of topics of TMF member networks highly increased over the last few years. Members include medical competence networks, networks dealing with rare diseases, psychotherapy networks, zoonosis networks, coordination centers for clinical trials, Fraunhofer institutes and, last not least, the German National Genome Research Network (NGFN).

The success of joint work within the TMF depends to a significant extent on the active input from its members in the topic-specific working groups. The working groups initiate projects, monitor their progress and actively drive them forward. This ensures that the TMF topics and results enjoy a broad consensus within the medical scientific community. At present there are seven active working groups within the TMF.

Newly founded in 2007 was the molecular medicine working group, which focuses on quality control for molecular data at various levels. Actually, this working group runs a project on "Quality Management for high-throughput genotyping".

National Genome Research Network

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National Genome Research Network

List of NGFN-Plus Integrated Consortia and NGFN-Transfer Innovation Alliances

IG Atherogenomics

Koordination: Prof. Dr.Heribert Schunkert

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Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Erklärung**
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Erdmann	Jeanette	PD Dr. rer. nat.	Universität zu Lübeck	A1, C1, C2, F1	A1 Polygenic and monogenic forms of MI
Linsel-Nitschke	Patrick	Dr. med.	Universität zu Lübeck	A2, D1, D2	A2 Genomics of coronary artery disease
Aherrarhou	Zouhair	Dr. med.	Universität zu Lübeck	B2	A3 Genomics of sub clinical atherosclerosis
Ehlers	Eva-Maria	PD Dr. med.	Universität zu Lübeck	B2	**B. Comparative Genomics**
Döhring	Lars	Dr. med.	Universität zu Lübeck	B2	B1 Syntenic regions for atherosclerosis in mice and humans
Fischer	Marcus	PD. Dr. med.	Universität zu Regensburg	A2, D2	B2 ABCC6 and arterial calcification
Hengstenberg	Christian	Prof. Dr. med.	Universität zu Regensburg	A1, C1, E1	**C. Population Genetics**
Teupser	Daniel	PD Dr. med.	Universität Leipzig	B1	C1 Cases and population platform (KORA/MONICA; GMIS;PREVENT-IT, LE HEART)
Thiery	Joachim	Prof. Dr. med.	Universität Leipzig	B1, C1,	C2 Genetic epidemiology methods platform
Blankenberg	Stefan	Prof. Dr. med.	Klinikum der Johannes Gutenberg-Universität	A3, D1, E1	**D. Functional Genomics**
Steller	Ulf	Dr. rer. nat.		E1	D1 Gene expression profiling Transcriptome of monocytes in subclinical atherosclerosis and MI patients
Koenig	Wolfgang	Prof. Dr. med.	Universitätsklinikum Ulm	A3, C1, E2	D2 Genomics of plasma lipids
König	Inke	PD Dr. rer. nat.	Universität zu Lübeck	C2	**E. Transfer**
Wichmann	Erich	Prof. Dr. rer. nat. Dr. med.	Helmholtz Zentrum München	C1	E1 SNP array for atherosclerosis Development of innovative diagnostics
Ziegler	Andreas	Prof. Dr. rer. nat.	Universität zu Lübeck	C2	E2 50 K Vascular Disease SNP Array

Meitinger	Thomas	Prof. Dr. med.	Helmholtz Zentrum München	CF	**F. Organisation**
					F1 Coordinating office
					Genotyping facility
					CF Genotyping/sequencing facility

IG Genetics of Heart Failure (Genetik der Herzinsuffizienz)

Koordination: Prof. Dr. Hugo A. Katus

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Pieske	Burkert	Prof. Dr.	Georg-August-Universität Göttingen	1	Genetic Risk of Heart Failure and its Subphenotypes
Hasenfuß	Gerd	Prof. Dr.	Georg-August-Universität Göttingen	1	Genetic Risk of Heart Failure and its Subphenotypes
Kääb	Stefan	Prof. Dr.	Ludwig-Maximilians-Universität München	1	Genetic Risk of Heart Failure and its Subphenotypes
Kreutz	Reinhold	Prof. Dr.	Charite Universitätsmedizin, CBF	2	Systems Biology Genomics of Left Ventricular Hypertrophy (LVH) using congenic rat models of polygenic hypertension
Hübner	Norbert	Prof. Dr.	Max-Delbrück-Centrum für molekulare Medizin	3	Gene Regulatory Networks in Cardiac Hypertrophy and Failure
Ivandic	Boris	Dr.	Universitätsklinikum Heidelberg	4	Genetic Modifiers of Heart Failure in Mice
Rottbauer	Wolfgang	PD Dr.	Universitätsklinikum Heidelberg	5	Functional Genomics in Zebrafish to Dissect the Genetics of Human Myocardial Disease
Frey	Norbert	PD Dr.	Universitätsklinikum Heidelberg	6	Novel Molecular Pathways in Cardiac Hypertrophy and Failure
Knöll	Ralph	Prof. Dr.	Georg-August-Universität Göttingen	7	Genetics and Functional Analysis of Cardiac Mechanosensation - Relevance for the Pathophysiology of Diastolic Heart Failure
Guan	Kaomei	Dr.	Georg-August-Universität	7	Genetics and Functional Analysis of Cardiac Mechanosensation -

			Göttingen		Relevance for the Pathophysiology of Diastolic Heart Failure
Lehnart	Stephan	Dr.	Georg-August-Universität Göttingen	8	Molecular Genomics Intracellular Calcium-Handling in Diastolic Dysfunction, Heart Failure and Arrhythmias
Pieske	Burkert	Prof. Dr.	Georg-August-Universität Göttingen	8	Molecular Genomics Intracellular Calcium-Handling in Diastolic Dysfunction, Heart Failure and Arrhythmias
Weis	Tanja	Dr.	Universitätsklinikum Heidelberg	9	Coordination Office
Stoll	Monika	Prof. Dr.	Leibniz-Institut für Arteriosklerose forschung an der Universität Münster	10	Genetic epidemiology of Heart Failure: Genetic Epidemiological Support for the IG
Eils	Roland	Prof. Dr.	Deutsches Krebsforschungszentrum	11	Bioinformatic Methods
Brors	Benedikt	Dr.	Deutsches Krebsforschungsentrum	11	Bioinformatic Methods
Katus	Hugo A.	Prof. Dr.	Universitätsklinikum Heidelberg	12	DNA-Platform
Meder	Benjamin	Dr.	Universitätsklinikum Heidelberg	12	DNA-Platform

IG Molekulare Mechanismen der Adipositas

Koordination: Prof. Dr. Johannes Hebebrand

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Hinney	Anke	Dr.	Universität Duisburg-Essen		Identification of human obesity genes with a focus on developmental aspects
Schürmann	Annette	Prof.	Deutsches Institut für Ernährungskunde (DIfE)		Identification and characterization of obesity genes, gene-gene and diet gene interactions involved in polygenic obesity in mice
Klingenspor	Martin	Prof.	Technische Universität München		Alterations of the mouse brain proteome associated with the early development of diet-induced obesity in the mouse
Stühler	Kai	Dr.	Ruhr-Universität Bochum		
Illig	Thomas	PD Dr.	Helmholtz Zentrum München		Evaluation of candidate genes for obesity and related disorders in large

			Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH)		representative epidemiological cohorts encompassing children and adults
Klingenspor	Martin	Prof.	Technische Universität München		Novel mouse models for the evaluation of candidate genes in the physiology of energy balance regulation
Rüther	Ulrich	Prof.	Heinrich-Heine-Universität Düsseldorf		Investigation of Fto as a major contributor to obesity
Sauer	Sascha	Dr.	Max-Planck-Institut für Molekulare Genetik (MPIMG)		Systematic molecular characterisation of compounds for prevention and therapy of obesity and insulin resistance
Blüher	Matthias	Prof.	Universität Leipzig		Adverse effects of weight cycling on longevity in rodents
Brockmann	Gudrun	Prof.	Humboldt-Universität zu Berlin		Implications of diet and exercise with interaction of allelic variations in the Berlin Fat Mouse line
Schäfer	Helmut	Prof.	Philipps-Universität Marburg		Central statistical genomics and data management
Scherag	André	Dr.	Universität Duisburg-Essen		
Hebebrand	Johannes	Prof.	Universität Duisburg-Essen		Coordination and quality management

IG Pathogenic role of mi-RNA in Herpes Infections

Koordination: Prof. Dr. Dr. Jürgen G. Haas

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Adler	Heiko	PD Dr.	Helmholtz-Zentrum	3	In vivo effects of miRNAs inthe murine herpesvirus 68 (mHV-68)
Grässer	Friedrich	Prof. Dr.	Universitätsklinik des Saarlandes	4	Function of EBV-encoded and EBV-induced mirRNA in latency and transformation
Meister	Gunther	Dr.	Max-Planck Institut	5	Identification of cellular targets of viral miRNAs
Förstemann	Klaus	Prof. Dr.	LMU	6	Biochemical interaction of viral and cellular miRNAs

Zimmer	Ralf	Prof. Dr.	LMU	7	Prediction of viral miRNAs targets

IG RNomics in Infections

Koordination: Prof. Dr. Jürgen Brosius

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Walter		PD Dr.	Deutsches Primatenzentrum Göttingen	3	
Brosius	Jürgen	Prof.	Universität Münster	4	

IG Systematic Genomics of Chronic Inflammatory Barrier Diseases

Koordination: Prof. Dr.Stefan Schreiber

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Schreiber	Stefan	Prof. Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	T7	Koordination
Franke	Andre	Prof. Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	GP 1	Genetische Ätiologie des M. Crohn
Rüther	Andreas	Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	GP 5	Genetische Ätiologie der atopischen Dermatitis
Fölster-Holst	Regina	PD Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	GP 5	Genetische Ätiologie der atopischen Dermatitis
Nebel	Almut	Prof. Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	GP 6	Genetische Ätiologie der Psoriasis
Weichenthal	Michael	PD. Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	GP 6	Genetische Ätiologie der Psoriasis
Nikolaus	Susanna	PD Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	GP 7	Genetische Ätiologie der Colitis ulcerosa

Schreiber	Stefan	Prof. Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	GP 8	Follow up Genotypisierung i.d. Teilprojekten GP 1, 2, 4-7
Till	Andreas	Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	GP 9	Funktionelle Aufklärung
Platzer	Matthias	PD Dr.	FLI- Leibniz-Institut für Altersforschung	GP 9	Funktionelle Aufklärung
Rosenstiel	Philip	Prof. Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	GP 10	Systematische Aufklärung von Signaltransduktionswegen: angeborene Immunität
Hofmann	Sylvia	Prof. Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	T1	Quätlitätsmanagenment
Schilhabel	Markus	Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	T1	Quätlitätsmanagenment
Rosenstiel	Philip	Prof. Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	T5	Hochdurchsatz zelluläre Screening Assays via Rna Interferenz
Krawczak	Michael	Prof. Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	T2	Genetisch-epidemiologische Unterstützung
Nothnagel	Reiner	Dr.	UNIKLINIK Schleswig-Holstein , Campus Kiel	T2	Genetisch-epidemiologische Unterstützung
Kabesch	Michael	PD Dr.	Ludwig-Maximilian-Universität München	GP 2	Genetische Ätiologie des Asthma bronchiale
Horstmann,	Rolf	Prof.	Bernhard-Nocht-Institut für Topenmedizin	GP 4	Genetischer Ätiologie der Tuberkulose
Meyer	Christian	Prof. Dr.	Bernhard-Nocht-Institut für Topenmedizin	GP 4	Genetischer Ätiologie der Tuberkulose
Lee	Young-Ae	Prof. Dr.	Charité, Campus Virchow-Klinikum	GP 5	Genetische Ätiologie der atopischen Dermatitis
Vingron	Martin	Prof. Dr.	Max Planck Institut für Molekulare Genetik (MPI-MG)	T 3	Bioinformatische Unterstützung

Albrecht	Mario	Dr.	Max Planck Institute für Informatik (MPI-INF)	T 3	Bioinformatische Unterstützung
Weidinger,	Stefan	PD Dr.	Technische Universität München, Klinikum Rechts der Isar	GP 5	Genetische Ätiologie der atopischen Dermatitis
Kaufman	Stefan H.E.	Prof. Dr.	Max Planck Institut für Infektionsbiologie	GP11	Systematische Aufklärung von Stoffwechelwegen: Adaptive Immunität
Wiemann	Stefan	PD Dr.	Deutsches Krebsforschungszentrum - DKFZ	T5	Hochdurchsatz zelluläre Screening Assays via RNA Interferenz

IG Functional and Translational Genomics of Acute Leukemias

Koordination: Prof. Dr. Christian Hagemeier

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Serve	Hubert	Prof.	Uni Frankfurt	TP3	
Hagemeier	Christian	Prof.	Charité	TP13, TP14, TP16	
Döhner	Hartmut	Prof.	Uni Ulm	TP1	
Thiede	Christian	Prof.	TU Dresden	TP2	
Müller-Tidow	Carsten	Prof.	Uni Münster	TP3	
Kulozik	Andreas	Prof.	Uni Heidelberg	TP4	
Marschalek	Rolf	Prof.	Uni Frankfurt	TP5	
Bohlander	Stefan	Prof.	LMU München	TP6, TP7	
Leutz	Achim	Prof.	MDC Berlin	TP8	
Duyster	Justus	Prof.	TU München	TP9	
Grez	Manuel	Prof.	GSH Frankfurt	TP10	
Neubauer	Andreas	Prof.	Uni Marburg	TP11	
Schrappe	Martin	Prof.	Uni Kiel	TP12	
Lottaz	Claudio	Dr.	Uni Regensburg	TP15	

IG Brain Tumor Network

Koordination: Prof. Dr. Peter Lichter

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Lichter	Peter	Prof. Dr.	DKFZ	SP-C	Koordinierung und Lenkung des Netzwerkes BTN^{plus}
Lichter	Peter	Prof. Dr.	DKFZ	SP-1	Hochdurchsatzanalyse von potentiellen Onkogenen und Tumorsuppressorgenen in Gliomen
Wolter	Marietta	Dr.	Heinrich-Heine-Universität	SP-2a	Aberrante miRNA-Expression in Gliomen: Molekulare Mechanismen, funktionelle Konsequenzen und deren klinische Signifikanz
Stühler	Kai	Dr.	Ruhr-Universität Bochum	SP-2b	Aberrante miRNA-Expression in Gliomen: Molekulare Mechanismen, funktionelle Konsequenzen und deren klinische Signifikanz
Brors	Benedikt	Dr.	DKFZ	SP-3	Modellierung und Bioinformatik
Hahn	Meinhard	Dr.	DKFZ	SP-4	Funktionelle Charakterisierung der an Hypoxie und Sauerstoffmetabolismus beteiligten Gene *Cited4* und *PRDX1*, die günstiges Therapieansprechverhalten und verbessertes Gesamtüberleben bei Gliompatienten vorhersagen
Acker	Till	Prof. Dr.	Universitätsklinikum Gießen und Marburg GmbH	SP-5	Selbsterneuerungs- und Differenzierungsmechanismen in Gliom-Stammzellen
Wick	Wolfgang	Prof. Dr.	DKFZ	SP-6a	Funktionelle Charakterisierung durch chronische nicht-lethale Hypoxie induzierter Invasions-assoziierter Proteine
Vajkoczy	Peter	Prof. Dr.	Charité - Medizinische Universität Berlin	SP-6b	Validierung hypoxie-regulierter Moleküle für Tumorinvasion und Angiogenese
Hau	Peter	Dr.	Universität Regensburg	SP-7	Dysregulierte Migration und Differenzierung - molekulare und zelluläre Dissektion von Krebsstammzellen in hochgradigen Gliomen
Waha	Andreas	Dr.	Universitätsklinikum Bonn	SP-8	Funktionelle Bedeutung epigenetisch deregulierter Gene in Gliomen
Angel	Peter	Prof. Dr.	DKFZ	SP-9a	Funktionelle Analyse der KLK-ADAM-Achse bei der

					Zellmigration und Invasion von humanen Gliomen
Pietsch	Torsten	Prof. Dr.	Universitätsklinikum Bonn	SP-9b	Funktionelle Analyse der KLK-ADAM-Achse in der Migration und Invasion von Glioblastomen
Roth	Wilfried	Dr.	DKFZ	SP-10	Neue Funktionen von BCL2-Familien-Proteinen: Invasivität und Autophagie
Reifenberger	Guido	Prof. Dr.	Heinrich-Heine-Universität	SP-11a	:Molekulare und funktionelle Charakterisierung von Genen, welche die Zellteilungs-symmetrie in malignen Gliomen kontrollieren
Radlwimmer	Bernhard	Dr.	DKFZ	SP-11b	Molekulare und funktionelle Charakterisierung von Genen, welche die Zellteilungs-symmetrie in malignen Gliomen kontrollieren
Herold-Mende	Christel	PD Dr.	Universität Heidelberg	SP-12a	Funktionelle Analysen von differenzierungsrelevanten Kandidatengenen in Gliomstammzellen
Radlwimmer	Bernhard	Dr.	DKFZ	SP-12b	Funktionelle Analysen von differenzierungsrelevanten Kandidatengenen in Gliom-Stammzellen
Hartmann	Christian	PD Dr.	DKFZ	SP-13	Funktionelle Charakterisierung der putativen Tumorsuppressorgene *EMP3* und *ST13* in Gliomen
Wick	Wolfgang	Prof. Dr.	Universität Heidelberg	SP-13	Funktionelle Charakterisierung der putativen Tumorsuppressorgene *EMP3* und *ST13* in Gliomen

IG Integrated Genome Network of Prostate Cancer

Koordination: PD Dr. Holger Sültmann

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Schlomm	Thorsten	Dr.	Martini-Klinik Prostatakrebszentrum und UKE Hamburg		Kollektivierung und Bereitstellung von klinischen Proben und Patientendaten
Simon	Ronald	PD Dr.	UKE Hamburg-Eppendorf		Biologische und klinische Signifikanz von Mikroamplifikationen im Prostatakarzinom
Yekebas	Emre	Prof. Dr.	UKE Hamburg-Eppendorf		Zytogenetische und molekulare Charakterisierung von Translokations-Bruchpunkten im Prostatakarzinom
Lehrach	Hans	Prof. Dr.	MPI für Molekulare Genetik		Analyse von Mutationen und epigenetischen Veränderungen im

					Prostatakarzinom
Sültmann	Holger	PD Dr.	Deutsches Krebsforschungszentrum		Splice-Varianten- und miRNA Expression in Tumoren
Brümmendorf	Tim	PD Dr.	UKE Hamburg-Eppendorf		Identifizierung klinisch relevanter Proteine im Prostatakarzinom
Heitmann	Alke	Dr.	Qiagen Hamburg GmbH		Entwicklung und Kommerzialisierung eines diagnostisch einsetzbaren Tools zur Detektion molekularer Marker im Prostatakarzinom
Haese	Alexander	PD Dr.	Martini-Klinik Prostatakrebszentrum und UKE Hamburg		Identifizierung und Validierung von diagnostischen und prognostischen Markern für die Therapieentscheidung beim Prostatakarzinom
Korf	Ulrike	Dr.	Deutsches Krebsforschungszentrum		Proteinarrays zur quantitativen Analyse von Proteinen in Tumoren und in Patientenseren
Weller	Horst	Prof. Dr.	Centrum für Angewandte Nanotechnologie (CAN) GmbH		Molekulare Tumor-Bildgebung mit Hilfe Antikörper-gekoppelter Nanopartikel
Mollenhauer	Jan	Prof. Dr.	Deutsches Krebsforschungszentrum		Funktionelle zelluläre Assays in Prostatakarzinom-Zelllinien
Sültmann	Holger	PD Dr.	Deutsches Krebsforschungszentrum		In vivo Analyse von Genen im Prostatakarzinom
Beissbarth	Tim	Dr.	Deutsches Krebsforschungszentrum		Bioinformatik und Systembiologie
Sültmann	Holger	PD Dr.	Deutsches Krebsforschungszentrum		Koordinierung, Kommunikation und Qualitätsmanagement

IG ENGINE (**E**xtended **N**euroblastoma **G**enome **I**nteraction **NE**twork)

Koordination: Prof. Dr. Angelika Eggert

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Berthold	Frank	Prof. Dr.	Klinikum der Universität zu Köln, Zentrum für Kinderheilkunde und Jugend-medizin	2	Central database & tumorbank
				8	Predictive gene signatures and trans-cription regulatory networks

Brors	Benedikt	Dr.	Deutsches Krebsforschungszentrum	7	Biostatistics for molecular trial design
Deubzer	Hedwig	Dr.	Deutsches Krebsforschungszentrum	3	Identification of NB initiating cells
				14	Targeting class I histone deacetylases
Eggert	Angelika	Prof. Dr.	Universitäts-Kinderklinik Essen	1	Project management
Eilers	Martin	Prof. Dr.	Philipps-Universität Marburg	11	Systematic drug testing
Fischer	Matthias	Dr.	Klinikum der Universität zu Köln, Zentrum für Kinderheilkunde und Jugendmedizin	8	Predictive gene signatures and transcription regulatory networks
Ivics	Zoltan	Dr.	Max-Delbrück-Centrum für Molekulare Medizin	5	Identification of NB initiating genes
König	Rainer	Dr.	Institut für Pharmazie und Molekulare Biotechnologie/Bioquant	12	Refined treatmend selection with machine learning techniques
Lawerenz	Christian		Deutsches Krebsforschungszentrum	2	Central database & tumorbank
Lode	Holger	Prof. Dr.	Charité Campus Virchow-Klinikum	15	Genetic vaccination
Oberthür	André	Dr.	Zentrum für Kinderheilkunde	9	NB Toponome
Savelyeva	Larissa	Dr.	Deutsches Krebsforschungszentrum	10	NB Fragilome
Schramm	Alexander	Dr.	Universitäts-Kinderklinik Essen	4	Proteomics of NB master regulators
				6	Role of microRNAs in NB pathogenesis
Schubert	Walter	Dr.	Otto-von-Guericke-Universität Magdeburg	9	NB Toponome
Schulte	Johannes H.	Dr.	Universitäts-Kinderklinik Essen	5	Identification of NB initiating genes
				6	Role of microRNAs in NB pathogenesis

Schwab	Manfred	Prof. Dr.	Deutsches Krebsforschungszentrum	10	NB Fragilome
				13	Targeting Myc functions
Stühler	Kai	Dr.	Ruhr-Universität Bochum	4	Proteomics of NB master regulators
Westermann	Frank	Dr.	Deutsches Krebsforschungszentrum	13	Targeting Myc functions
Witt	Olaf	Prof. Dr.	Deutsches Krebsforschungszentrum	3	Identification of NB initiating cells
				14	Targeting class I histone deacetylases

IG Deciphering Oncogene Dependencies in Human Cancer Oncogene Mutation Space

Koordination: Dr. Roman Thomas

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Nürnberg	Peter	Prof. Dr.	University of Cologne	1	Evaluation of tools for clinical detection of mutations and copy number changes
Wolf	Jürgen	Prof. Dr.	University Clinic Cologne	2	Analysis of patient mutation space and clinical outcome
Thomas	Roman	Dr.	Max-Planck-Institute	3	Systematic high-throughput analysis of oncogenicity of human oncogene mutations
Ahmadian	Reza	PD Dr.	Heinrich-Heine Universtity Hospital	4a	Functional impact of oncogene mutants and small molecules on the Ras and Rho signaling pathways
Wittinghofer	Alfred	Prof. Dr.	MPI für molekulare Physiologie	4b	Functional impact of oncogene mutants and small molecules on the Ras and Rho signaling pathways
Rauh	Daniel	Dr.	Max Planck Society	5a	Dissection of oncogene dependencies by small organic molecule perturbations
Waldmann	Herbert	Prof. Dr.	Max Planck Institute	5b	Dissection of oncogene dependencies by small organic molecule perturbations
Rahnenführer	Jörg	Prof. Dr.	University Dortmund	6a	Statistical modeling of drug response and pathway alterations
Lengauer	Thomas	Prof. Dr. Dr.	MPI für Informatik	6b	Statistical modeling of drug response and pathway alterations

IG Systems Biology of Genetic Diseases, Mutanom

Koordination: Prof. Dr. Hans Lehrach

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Lehrach	Hans	Prof. Dr.	Max-Planck-Institut für Molekulare Genetik	1	Project coordination
Schweiger	Michal	Dr.	Max-Planck-Institut für Molekulare Genetik	2	Mutational analysis
Mollenhauer	Jan	Prof. Dr.	Medical Biotechnology Center University of Southern Denmark	3	Recombinant cancer cell libraries & drug target recovery
Sültmann	Holger	PD Dr.	German Cancer Research Center (DKFZ)	4	Quantification of cancer pathways
Wanker	Erich	Prof. Dr.	Max-Delbrück-Centrum für Molekulare Medizin	5	Protein interaction networks
Schultze-Motel	Paul	Dr.	Max-Delbrück-Centrum für Molekulare Medizin	5	Protein interaction networks
Schäfer	Reinhold	Prof.	Charité Universitätsmedizin Berlin	6	Cellular signalling networks
Herrmann	Bernhard	Prof.	Max-Planck-Institut für Molekulare Genetik	7	Mouse disease models
Markus	Morkel	Prof.	Max-Planck-Institut für Molekulare Genetik	7	Mouse disease models
Lange	Bodo	PD Dr.	Max-Planck-Institut für Molekulare Genetik	8	Protein complex composition and function in disease
Herwig	Ralf	Dr.	Max-Planck-Institut für Molekulare Genetik	9	Data integration and modelling
Drewes	Gerard	Dr.	Cellzome AG	10	Quantitative Proteomics

IG Translational Genome Research Network in Pancreatic Cancer

Koordination: Prof. Dr. Thomas M. Gress

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Gress	Thomas M.	Prof. Dr.	Philipps-Universität Marburg	TP3, TP11, TP Koord	TP3, TP11, TP Koordination
Buchholz	Esther		Philipps-Universität Marburg	TP Koord	TP3, TP11, TP Koordination
Büchler	Markus	Prof. Dr.	Universitätsklinikum Heidelberg	TP1	Klinische Ressourcen und Daten
Giese	Nathalia	Dr.	Universitätsklinikum Heidelberg	TP1	Klinische Ressourcen und Daten
Schmid	Roland M.	Prof. Dr.	TU München	TP2	Mausmodelle des Pankreaskarzinoms
Buchholz	Malte	PD Dr.	Philipps-Universität Marburg	TP3, TP11	TP3 Parallelisierte funktionelle Charakterisierung, TP11 Molekulare Differentialdiagnose
Seufferlein	Thomas	Prof. Dr.	Martin-Luther-Universität Halle-Wittenberg	TP4	Kinasenetzwerke im Pankreaskarzinom
Hoheisel	Jörg	Dr.	DKFZ Heidelberg	TP5, TP12	TP5 Quantitative Analyse von Proteininteraktionen, TP12 Epigenetische Analyse zur therapeutischen Patienten-Stratifizierung
Hahn	Stephan	Prof. Dr.	Ruhr-Universität Bochum		MiRNAs als therapeutische Targets für das Pankreaskarzinom
Friess	Helmut	Prof. Dr.	TU München	TP7	Molekulare Analyse der tumorspezifischen Stromaaktivierung
Kleeff	Jörg	PD Dr.	TU München	TP7	Molekulare Analyse der tumorspezifischen Stromaaktivierung
Schwarte-Waldhoff	Irmgard	PD Dr.	Ruhr-Universität Bochum	TP9	Entwicklung von molekulardiagnostischen Verfahren zur Früherkennung des Pankreaskarzinoms basierend auf sezernierten/freigesetzten Kandidaten-Proteinen

IG Modifiers of Intestinal Tumor Formation and Progression

Koordination: Prof. Dr. Bernhard Herrmann

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Schweiger	Michal	Dr.	Max-Planck-Institut für molekulare Genetik	1	Analyse von normalem und Darmtumorgewebe und Validierungsexperimente in menschlichen Zelllinien
Herrmann	Bernhard	Prof.Dr.	Max-Planck-Institut für molekulare Genetik	2	Identifizierung und Feinkartierung von Modulatoren der epigenetischen Genkontrolle und APC-Min induzierter Darmtumore in CSS Mausstämmen
Lehrach	Hans	Prof. Dr	Max-Planck-Institut für molekulare Genetik	3	Immunpräzipitation von methylierter DNA und Gen-Expressionsanalyse mittels der Sequenziertechnik der 2. Generation
Walter	Jörn	Prof.Dr.	Universität des Saarlandes, Campus Saarbrücken	4	Entwicklung einer Bisulphit-Hochdurchsatz-Sequenzierungsplatform in Kombination mit integrierter Bioinformatik
Morkel	Markus	Dr.	Max-Planck-Institut für molekulare Genetik	5	Validierung von Kandidatengenen (Modifier) in transgenen Mausmodellen
Herwig	Ralf	Dr.	Max-Planck-Institut für molekulare Genetik	6	Bioinformatik und Datenintegration

IG Integrated Genomic Investigation of Colorectal Carcinoma (CRC)

Koordination: Prof. Dr. Kari Hemminki

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Hampe	Jochen	PD Dr.	Universitätsklinikum Schleswig-Holstein		Fine mapping + replication
Hemminki	Kari	Prof. Dr.	Deutsches Krebsforschungszentrum		Population-based studies
Schafmayer	Clemens	Dr.	Universitätsklinikum Schleswig-Holstein		Population-based and prospective validation
Chang-Claude	Jenny	Prof. Dr.	Deutsches Krebsforschungszentrum		Population-based and prospective validation

Brenner	Hermann	Prof. Dr.	Deutsches Krebsforschungszentrum		Population-based and prospective validation
Burwinkel	Barbara	PD Dr.	Deutsches Krebsforschungszentrum		Population-based and prospective validation
Krawczak	Michael	Prof. Dr.	Universitätsklinikum Schleswig-Holstein		Statistics and Genetic epidemiology
Brosch	Mario	Dr.	Universitätsklinikum Schleswig-Holstein		Somatic mutation signature
Platzer	Matthias	Dr.	Leibniz-Institut für Altersforschung		Somatic mutation signature
Siebert	Reiner	Prof. Dr.	Universitätsklinikum Schleswig-Holstein		Somatic genomic imbalances, LOH and methylation
Boutros	Michael	Dr.	Deutsches Krebsforschungszentrum		Pathways - cellular models
Spang	Rainer	Prof. Dr.	Universität Regensburg		System biology of the cancer cell
Kalthoff	Holger	Dr.	Universitätsklinikum Schleswig-Holstein		Pathways: tumor tissue
Hemminki	Kari	Prof. Dr.	Deutsches Krebsforschungszentrum		Coordination

IG MooDS: Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia

Koordination: Prof. Dr. Markus Nöthen

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Cichon	Sven	PD Dr. rer. nat.	Universitätsklinikum Bonn	1	Genomik bei Bipolarer Störung
Schumacher	Johannes	PD Dr. med.	Genetic Basis of Mood and Anxiety Disorders	1	Genomik bei Bipolarer Störung
Holsboer	Florian	Prof. Dr. med. Dr. rer. nat.	Max Planck Institut für Psychiatrie	1	Genomik bei unipolarer Störung
Lucae	Susanne	Dr. med. univ. Dr. rer. nat.	Max Planck Institut für Psychiatrie	2	Genomik bei unipolarer Störung

Rujescu	Dan	PD Dr. med.	Psychiatrische Klinik der LMU	3	Genomik bei Schizophrenie
Maier	Wolfgang	Prof. Dr. med.	Universitätsklinikum Bonn	3	Genomik bei Schizophrenie
Nöthen	Markus	Prof. Dr. med.	Universitätsklinikum Bonn	4a	Hochdurchsatz-Genotypisierung
Bettecken	Thomas	Dr. rer. nat.	Max Planck Institut für Psychiatrie	4b	Hochdurchsatz-Genotypisierung
Rietschel	Marcella	Prof. Dr. med.	Zentralinstitut für Seelische Gesundheit	5	MooDS Phenom Datenbank und Reverse Phänotypisierung
Reinelt	Gerhard	Prof. Dr. med.	Universität Heidelberg	5	MooDS Phenom Datenbank und Reverse Phänotypisierung
Schulze	Thomas G.	PD Dr. med.	Unit on the Genetic Basis of Mood and Anxiety Disorders	5	MooDS Phenom Datenbank und Reverse Phänotypisierung
Meyer-Lindenberg	Andreas	Prof. Dr. med. Dipl. math.	Zentralinstitut für Seelische Gesundheit	6a	Imaging Genetik
Walter	Henrik	Prof. Dr. med. Dr. phil.	Universitätsklinikum Bonn	6b	Imaging Genetik
Heinz	Andreas	Prof. Dr. med.	Charité–Universitätsmedizin Berlin	6c	Imaging Genetik
Wienker	Thomas F.	Prof. Dr. med.	Universitätsklinikum Bonn	7	Statistische Analysen zu genomweiten Assoziationsstudien
Müller-Myhsok	Bertram	Prof. Dr. med.	Max Planck Institut für Psychiatrie	8	Entwicklung statistischer Methoden für komplexe Gen-Gen Interaktionen in genomweiten Datensätzen
Cichon	Sven	PD Dr. rer. nat.	Universitätsklinikum Bonn	9	Allel-spezifische Expression
Becker	Albert	Prof. Dr. med.	Universitätsklinikum Bonn	9	Allel-spezifische Expression
Brors	Benedikt	Dr. rer. nat.	Universität Heidelberg	10	Methodenentwicklung für biologische Pathway-Informationen in GWA-Analysen
Wanker	Erich E.	Prof. Dr. rer. nat.	Max-Delbrueck-Center für Molekulare Medizin Berlin-Buch	11	Protein-Protein Interaktions-Netzwerk

Zimmer	Andreas	Prof. Dr. rer. nat.	Universitätsklinikum Bonn	12a	Funktionelle Untersuchungen mit Hilfe von transgenen Mausmodellen und Proteomanalysen
Wurst	Wolfgang	Prof. Dr. rer. nat.	Helmholtz Zentrum München	12b	Funktionelle Untersuchungen mit Hilfe von transgenen Mausmodellen und Proteomanalysen
Turck	Chris	Prof. Dr. rer. nat.	Max Planck Institut für Psychiatrie	12c	Funktionelle Untersuchungen mit Hilfe von transgenen Mausmodellen und Proteomanalysen
Raff	Ruth	Dr. rer. nat.	Universitätsklinikum Bonn	14	Projekt-Management und Graduierten-Training

IG Genetics of Alcohol Addiction

Koordination: Prof. Dr. Rainer Spanagel

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Spanagel	Rainer	Prof.Dr	Central Institute of Mental Health		Coordination Consortium
Eils	Roland	Prof.Dr	German Cancer Research Center		Gene data mining platform and statistics
Brors	Benedikt	Dr.	German Cancer Research Center		siehe Eils
Wienker	Thomas	Prof.Dr	University of Bonn		siehe Eils
Matthäus	Franziska	Dr.	University of Heidelberg,		Mathematical Modelling and Analysis
Jäger	Willi	Prof. Dr. Dr. h.c. mult	University of Heidelberg,		siehe Matthäus
Schütz	Günter	Dr. med.	German Cancer Research Center (DKFZ)		Functional analysis I and conditional mouse models
Wurst	Wolfgang	Prof.Dr	GSF - National Research Center for Environment and Health,		Functional analysis II and RNAi in vivo application
Deussing	Jan	Dr.	Max Planck Institute of Psychiatry		siehe Wurst
Zimmer	Andreas	Prof.Dr	University of Bonn		Functional analysis III
Bartsch	Dusan	Prof.Dr	Central Institute of Mental Health		Transgenic rat models

Gebicke-Haerter	Peter	Prof.Dr	Central Institute of Mental Health		Glutamatergic and epigenetic profiling with microarrays
Hoheisel	Jörg	Prof.Dr	Deutsches Krebsforschungszentrum		siehe Gebicke-Haerter
Rietschel	Marcella	Prof.Dr	Central Institute of Mental Health		GWA studies in alcohol dependent patients and replication studies
Nöthen	Markus	Prof.Dr	University of Bonn		siehe Rietschel
Dahmen	Norbert	PD Dr.	Universität Mainz		GWA studies in population-based samples for high versus low alcohol consumption and replication studies
Wichmann	H.Erich	Prof.Dr	GSF Institute of Epidemiology		siehe Dahmen
Heinz	Andreas	Prof.Dr	University Medical Center Berlin, Campus Charité		Endophenotyping with fMRI: Genetic modulation and treatment response
Walter	Henrik	Prof.Dr	University Clinic Bonn,		siehe Heinz
Kiefer	Falk	Prof.Dr	Central Institute of Mental Health		siehe Heinz
Mann	Karl	Prof.Dr Dr.	Central Institute of Mental Health		Endophenotyping with spectroscopy: Genetic modulation and treatment response
Ende	Gabriele	Dr.	Central Institute of Mental Health		siehe Mann
Gallinat	Jürgen	PD Dr.	Psychiatry, Charité, CCM		siehe Mann
Sartorius	Alexander	Dr.	Central Institute of Mental Health		Glutamate spectroscopy at 9.4T combined with microdialysis in rodents

IG German Mental Retardation Network (Netzwerk Mentale Retardierung)

Koordination: Prof. Dr. André Reis

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Rauch	Anita	PD Dr. med.	Friedrich-Alexander-Universität Erlangen-Nürnberg	1	MR Zentrum Erlangen
Ropers	Hans-Hilger	Prof. Dr. med.	Max Planck Institut für Molekulare Genetik	2	MR Zentrum Berlin

Riess	Olaf	Prof. Dr. med.	Eberhard-Karls-Universität Tübingen	3	MR Zentrum Tübingen
Strom	Tim M	PD Dr. med.	Helmholtz Zentrum München, Deutsches Forschungs-zentrum für Gesundheit und Umwelt (GmbH)	4	MR Zentrum München
Engels	Hartmut	Dr. rer. nat.	Rheinische Friedrich-Wilhelms-Universität Bonn	5	MR Zentrum Bonn
Wieacker	Peter	Prof. Dr. med.	Medizinische Fakultät der Westfälischen Wilhelms-Universität Münster	6	MR Zentrum Münster
Schröck	Evelin	Prof. Dr. med.	Medizinische Fakultät Carl Gustav Carus der Technischen Universität Dresden	7	MR Zentrum Dresden
Wieczorek	Dagmar	PD Dr. med.	Universität Duisburg Essen	8	MR Zentrum Essen
Rappold	Gudrun	Prof. Dr. rer. nat.	Ruprechts-Karls Universität Heidelberg	9	MR Zentrum Heidelberg
Schenck	Annette	Dr. rer. nat.	Radboud Universität Nijmegen	10	Modellierung mentaler Retardierung in Fliegen
Reis	André	Prof. Dr. med.	Friedrich-Alexander-Universität Erlangen-Nürnberg	11	Projektkoordination

IG Epilepsy and Migraine Integrated Network (EMINet)

Koordination: Prof. Dr. Christian Kubisch

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Dichgans	Martin	Prof. Dr.	LMU Munich	2	Whole-genome association study in migraine without aura and functional characterization of disease associated alleles (TP2)

Sander	Thomas	Dr.	University of Cologne	3	Genome-wide association mapping of gene configurations conferring risk to idiopathic generalized epilepsies (TP3)
Nürnberg	Peter	Prof. Dr.	University of Cologne	4	High-throughput sequencing of functional and positional candidate genes for common forms of migraine and epilepsy (TP4)
Schoch-McGovern	Susanne	Dr.	University of Bonn	5	Genetic basis of Levetiracetam pharmacoresistance and side effects in human epilepsy (TP5)
Lerche	Holger	Prof. Dr.	University of Ulm	6	Functional analysis of human ion channel mutations in cellular and animal models (TP6)
Becker	Albert	PD Dr.	University of Bonn		Aberrant transcriptional networks in human epileptic tissue
Beck	Heinz	Prof. Dr.	University of Bonn		Mechanisms underlying the development of cellular hyperexcitability in mouse models of human epilepsy
Isbrandt	Dirk	Dr.	University of Hamburg	9	Subthreshold ion channels in epileptogenesis and neuronal synchronization

IG Gene Identification and Functional analyses in Alzheimer's disease

Koordination: PD Dr. Matthias Riemenschneider

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Riemenschneider	Matthias	PD Dr	Klinikum Rechts der Isar, TU-München	1	Identification of genetic factors in Alzheimer's disease
Krobitsch	Sylvia	Dr	Max Plank Institut für molekulare Genetik	2	Identification and functional characterization of novel early-onset Alzheimer's genes
Haas	Christian	Prof. Dr.	LMU München	3	The physiological function of BACE1-is BACE1 a safe therapeutic target?
Garratt	Alistair	Dr	Max-Delbrück-Centrum für Molekulare Medizin (MDC) Berlin-Buch	3	The physiological function of BACE1-is BACE1 a safe therapeutic target?

Müller	Ulrike	Prof. Dr.	University of Heidelberg	4	In vivo analysis of APP functional domains-can we safely abrogate APP/APLP processing?
Hartmann	Tobias	Prof. Dr.	Universität des Saarlandes	5	Functional involvement of Alzheimer's disease candidate risk genes in lipid homeostasis, Ab metabolism and Ab response
Endres	Kristina	Dr.	Johannes Gutenberg Univers. Mainz	6	Regulation of ADAM10 gene expression and neuroprotection
Jucker	Mathias	Prof. Dr.	Hertie-Institut für klinische Hirnforschung	7	Pathomechanism of Cerebral Amyloid Angiopathy
Wanker	Erich	Prof. Dr.	Max-Delbrück-Centrum für Molekulare Medizin (MDC) Berlin-Buch	8	Identification and characterization of modulators of Alzheimer's disease pathogenesis
Wurst	Wolfgang	Prof. Dr.	Helmholtz Zentrum München	9	Animal models for candidate genes of Alzheimer's disease
Riemenschneider	Matthias	PD Dr	Klinikum Rechts der Isar, TU-München	10	Scientific administration office of the AD-IG

IG Functional Genomics of Parkinson's disease

Koordination: Prof. Dr. Thomas Gasser

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Gasser	Thomas	Prof. Dr.	Eberhard-Karls-Universität Tübingen	TP1/TP2	Scientific Coordinating Office
Klein	Christine	Prof. Dr.	Universität Lübeck	TP3	Mutations in recessive Parkinson's disease genes
Höglinger	Günther	PD. Dr.	Philipps-Universität Marburg	TP4	Genome-wide siRNA screen in an a-synuclein-based in vitro model of Parkinson's disease
Schulz	Jörg B.	Prof. Dr.	Universität Göttingen	TP5	Modifier screen in flies overexpressing LRRK2
Zweckstetter	Markus	Prof. Dr.	Universität Göttingen	TP6	Molecular mechanisms of pathogenic misfolding of a-synuclein
Auburger	Georg	Prof. Dr.	J.W. Goethe University	TP7	Biomarkers of the common Parkinson pathway:a-Synuclein induction and synaptic pathology in recessive PD
Riess	Olaf	Prof. Dr.	Eberhard-Karls-	TP8	Calpain cleavage of a-synuclein in the pathogenesis

			Universität Tübingen		of Parkinson's disease by cell culture and animal models
Kahle	Philipp	Prof. Dr.	Eberhard-Karls-Universität Tübingen	TP9	Regulation of Apoptosis Signal Regulating Kinase Pathways by DJ-1 and Parkin
Krüger	Rejko	Prof. Dr.	Eberhard-Karls-Universität Tübingen	TP10	Mitochondrial stress response in neurodegeneration and aging: OMI and DJ-1 mediated signalling pathways
Winklhofer	Konstanze	PD. Dr.	Ludwig-Maximilians-Universität München	TP11	The physiological and pathological function of PINK 1, parkin and LRRK2 in zebrafish and other models
Ueffing	Marius	PD. Dr.	TU München	TP12	Functional characterization of LRRK2 in mammalian cells and tissues
Liss	Birgit	Prof. Dr.	Universität Ulm	TP13	Dopaminergic dysfunction and molecular pathways to selective neurodegeneration: from mouse models to Parkinson disease.
Schütz	Günther	Prof. Dr.	German Cancer Research Center	TP14	Characterization of genetic mouse models for Parkinson´s disease
Marcus	Katrin	Prof. Dr.	Ruhr University Bochum	TP15	Core facility: High-performance proteome analysis for biomarker discovery and elucidation of pathomechanisms
Zell	Andreas	Prof. Dr.	Eberhard-Karls-Universität Tübingen	TP16	Core facility: Bioinformatics: data integration towards a systems level model of Parkinson's disease Generation of a systems biology model
Meitinger	Thomas	Prof. Dr.	Helmholtz Zentrum München	Core facility	Core facility: High throughput genotyping

IG NeuroNet - Verbundprojekt Neurodegeneration

Koordination: Prof. Dr. Erich Wanker

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Wanker	Erich	Prof. Dr.	Max-Delbrück-Centrum für Molekulare Medizin	1	Protein-Protein Interaktionsnetzwerke bei neurodegenerativen Erkrankungen
Selbach	Matthias	Dr.	Max-Delbrück-Centrum für Molekulare Medizin	2	Protein Interaktionsscreening durch quantitative Massen-spektroskopie

Stelzl	Ulrich	Dr.	Max-Planck-Institut für Molekulare Genetik	3	Modulation von Protein-Protein Wechselwirkungen durch Phosphorylierung
Priller	Josef	Prof. Dr.	Charité - Universitätsmedizin Berlin	4	Klassifikation von Phänotyp-Genotyp-Beziehungen bei - neurodegenerativen Erkrankungen
Lange	Bodo	PD Dr.	Max-Planck-Institut für Molekulare Genetik	5	Modulation von Proteinkomplexkomposition und Funktion durch Stress und Neurodegenerative Krankheitssignale
Nietfeld	Wilfried	Dr.	Max-Planck-Institut für Molekulare Genetik	6	Erstellung von Genexpressionssignaturen von neurodegenerativen Krankheitsprozessen
Boutros	Michael	Dr.	Deutsches Krebsforschungszentrum	7	Systematische Analyse von Phänotypen mittels RNAi und kleinen Molekülen
Bork	Peer	Prof. Dr.	European Molecular Biology Laboratory	8	Datenintegration und Erstellung von Phänotyp-Protein-Wirkstoff Netzwerken
Andrade	Miguel	Dr.	Max-Delbrück-Centrum für Molekulare Medizin	8	Datenintegration und Erstellung von Phänotyp-Protein-Wirkstoff Netzwerken

IG From Disease genes to Protein Pathways (DiGTOP)

Koordination: Prof. Dr. Wolfgang Wurst

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Stewart	Francis	Prof. Dr.	Technische Universität Dresden		Genidentifikation und DNA Konstruktproduktion
von Melchner	Harald	Prof. Dr.	Universität Frankfurt		In situ Markierung von Krankheitsproteinen in embryonalen Stammzellen mit Genfallen-induzierten Mehrzweckallelen
Wurst	Wolfgang	Prof. Dr.	HelmholtzZentrum München		Produktion proteinmarkierter pluripotenter und differenzierter ES Zellen
Hyman	Tony	Prof. Dr.	MPI für Zellbiologie und Genetik Dresden		Produktion und Imaging von HeLa und ES Zelllinien
Brüstle	Oliver	Prof. Dr.	Universität Bonn		Etablierung und Analyse transgener hES Zelllinien und neuralen Stammzelllinien
Mann	Matthias	Prof. Dr.	MPI für Biochemie,		Proteininteraktionsstudien mittels

			Martinsried		massenspektrometriebasierter Proteomik in in vitro und in vivo Systemen
Gibson	Toby	Prof. Dr.	EMBL Heidelberg		DiGtoP bioinformatics – resource development and application in comparative network analysis
Kühn	Ralf	Dr.	HelmholtzZentrum München		Mausmodelle für die in vivo Validierung von Proteininteraktionen
Buchholz	Frank	Dr.	MPI für Zellbiologie und Genetik Dresden		Validierung und Zergliederung der Signalwege von Krankheitsrelevanten Genen mit endoribonucelase präparierter siRNA
Wurst	Wolfgang	Prof. Dr.	HelmholtzZentrum München		Management & Training

IG German Mouse Clinic (GMC)

Koordination: Prof. Dr. Martin Hrabé de Angelis

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Hrabé de Angelis	Martin	Prof. Dr.	Helmholtz Zentrum München	1	Core Facility
Gailus-Durner	Valérie	Dr.	Helmholtz Zentrum München	1	Core Facility
Fuchs	Helmut	Dr.	Helmholtz Zentrum München	1	Core Facility
Wolf	Eckhard	Prof.	Genzentrum der LMU München	2	Clinical Chemical Screen
Wurst	Wolfgang	Prof.	Helmholtz Zentrum München	3	Behavioral Screen
Hölter-Koch	Sabine	Dr.	Helmholtz Zentrum München	3	Behavioral Screen
Klopstock	Thomas	PD Dr. med.	LMU München	4	Neurological Screen
Graw	Jochen	Prof.	Helmholtz Zentrum München	5	Eye Screen
Hrabé de Angelis	Martin	Prof.	Helmholtz Zentrum München	6	Dysmorphology Screen
Fuchs	Helmut	Dr.	Helmholtz Zentrum München	6	Dysmorphology Screen
Busch	Dirk	Prof.	TU München	7	Immunology Screen
Ollert	Markus	Prof.	TU München	8	Allergy Screen

Adamski	Jerzy	Prof.	Helmholtz Zentrum München	9	Steroid Screen
Zimmer	Andreas	Prof.	Universitätsklinikum Bonn	10	Nociceptive Screen
Schulz	Holger	Prof.	Helmholtz Zentrum München	11	Lung Function Screen
Stöger	Tobias	Dr.	Helmholtz Zentrum München	11	Lung Function Screen
Beckers	Johannes	PD Dr.	Helmholtz Zentrum München	12	Molecular Phenotyping Screen
Klingenspor	Martin	Prof.	TU München	13	Energy Metabolism Screen
Daniel	Hannelore	Prof.	TU München	13	Energy Metabolism Screen
Katus	Hugo	Prof.	Universität Heidelberg	14	Cardiovascular Screen
Ivandic	Boris	Dr.	Universität Heidelberg	14	Cardiovascular Screen
Höfler	Heinz	Prof.	Helmholtz Zentrum München	15	Pathology Screen
Esposito	Irene	PD Dr.	Helmholtz Zentrum München	15	Pathology Screen
Hrabé de Angelis	Martin	Prof.	Helmholtz Zentrum München	16	Data Management
Lengger	Christoph	Dr.	Helmholtz Zentrum München	16	Data Management
Schughart	Klaus	Prof.	HZI - Helmholtz-Zentrum für Infektionsforschung	17	Host Pathogen Interaction Screen
Hrabé de Angelis	Martin	Prof.	Helmholtz Zentrum München	18	EMMA
Hagn	Michael	Dr.	Helmholtz Zentrum München	18	EMMA

IG MHC Haplotype Sequencing: An Integrated Approach to Common Disease

Koordination: Dr. Margret Hoehe

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Hoehe	Margret	Dr.	MPI-MG Berlin		MHC-Haplotypen-Sequenzierung

IG Cellular Systems Genomics in Health and Disease

Koordination: PD Dr. Stefan Wiemann

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Bechtel	Stefanie	Dr.	DKFZ Heidelberg		Functional Genomic Resources for NGFNplus
Wiemann	Stefan	PD Dr.	DKFZ Heidelberg		Cellular Screening Systems
Stauber	Roland	Prof.	Klinikum Mainz		Transport Biosensors
Arlt	Dorit	Dr.	DKFZ Heidelberg		Signalling Network analysis
Gavin	Anne-Claude	Dr.	EMBL Heidelberg		TAP - Protein interaction mapping
Pepperkok	Rainer	Dr.	EMBL Heidelberg		Protein and Network dynamics
Korf	Ulrike	Dr.	DKFZ Heidelberg		Quantitative Proteinarrays
Kögl	Manfred	Dr.	DKFZ Heidelberg		Functional Validation of Protein Interactions
Lange	Bodo	PD Dr.	Max-Planck Institut für Molekulare Genetik		Primary Cancer Cell Models
Schneeweiss	Andreas	Prof. Dr.	Uniklinik Heidelberg		Clinical validation
Beissbarth	Tim	Dr.	DKFZ Heidelberg		Pathway reconstruction & modelling
Rosenfelder	Heiko		DKFZ Heidelberg		Integrated bioinformatics
Wiemann	Stefan	PD Dr.	DKFZ Heidelberg		QM & Standards

IA Entwicklung prophylaktisch wirksamer Anti-Malaria Verbindungen

Koordination: Dr. Birte Sönnichsen

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Sönnichsen	Birte	Dr.	Cenix BioScience GmbH		Anti Malaria Zielgene und Wirkstoffkandidaten
Matuschewski	Kai	Dr.	Universität Heidelberg		Zielgene im Parasiten
Frischknecht	Friedrich	Dr.	Universität Heidelberg		Imaging von interaktionen des Parasiten mit Leberzellen

IA Breast Cancer Kit

Koordination: Prof. Dr. Jan Georg Hengstler

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Schmidt	Marcus	Dr. med.	Universität Mainz	1	
Gehrmann	Mathias	Dr.	Siemens Medical Solutions Diagnostic GmbH	2	
Hengstler	Jan Georg	Prof. Dr. med.	Institut für Arbeitsphysiologie an der Technischen Universität Dortmund	3	Oncoprofile-Kit

IA Heart Failure Therapy

Koordination: Prof. Dr. Markus Hecker

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Henning	Stefan	Dr.	AVONTEC GmbH	1	
Hecker	Markus	Prof. Dr.	Universität Heidelberg	2	
Wagner	Andreas H.	Priv.-Doz. Dr.	Universität Heidelberg	2	
Müller	Oliver J.	Dr. med.	Universität Heidelberg	3	

Bekeredjian	Raffi	PD Dr. med.	Universität Heidelberg	3	

IA Metabolomics in Heart Failure as a Novel Diagnostic Tool

Koordination: Prof. Dr. Hugo A. Katus

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Katus	Hugo A.	Prof. Dr.	Universitätsklinikum Heidelberg	1	Novel Biomarkers for Heart Failure - Metabolic Signatures
Fuhrmann	Jens	Dr.	metanomics GmbH	1	Novel Biomarkers for Heart Failure - Metabolic Signatures
Frey	Norbert	PD Dr.	Universitätsklinikum Heidelberg	2	Metabolic Profiling in Mouse Models of Heart Failure
Ivandic	Boris	Dr.	Universitätsklinikum Heidelberg	2	Metabolic Profiling in Mouse Models of Heart Failure
Weis	Tanja	Dr.	Universitätsklinikum Heidelberg		Coordination

IA New Tools for the Prevention of Cardiovascular Diseases and Disorders in Chronic Kidney Disease

Koordination: Prof. Dr. Joachim Jankowski

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Jankowski	Vera	Dr.	Charité – Universitätsmedizin Berlin	1	Bioanalytik der chronischen Niereninsuffizienz
Lehmann	Kerstin	Dr.	Charité – Universitätsmedizin Berlin	2	Effekte auf aktivierte Endothelzellen
Buschmann	Ivo	PD Dr.	Charité – Universitätsmedizin Berlin	2	Effekte auf aktivierte Endothelzellen
Herget-Rosenthal	Stefan	PD Dr.	Universitätsklinikum Essen / Universität Duisburg Essen	3	Patienten und Proben
Herwig	Ralf	Dr.	Max Planck Institut für Molekulare Genetik (MPIMG)	4	Bioinformatik
Lemke	Horst-Dieter	Dr.	EXcorLab GmbH	5	Aktivierung von Neutrophilen durch urämische Proteine
Krahn	Thomas	Dr.	Bayer Schering Pharma	6	CVD Drug Discovery Biomarker & Targets

IA Proteinanalysen in FFPE Brustkrebsgeweben - Brustkrebsmarker

Koordination: Prof. Dr. Karl-Friedrich Becker

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Becker	Karl-Friedrich	Prof. Dr.	Technische Universität München		Proteinlysat Mikroarrayanalyse für uPA und PAI-1 von Formalin-fixierten Brustkrebsgeweben
					HER2-Rezeptor Expression und Signalwege in Brustkrebsgeweben
Porschewski	Peter	Dr.	Qiagen GmbH		Proteomsignaturen in FFPE-Geweben

IA Subgenome Fraktionation for High Throughput Sequencing

Koordination: Dr. Bernhard Korn

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Beier	Markus	Dr.	febit AG		Development of microarrays for sub-genome preparation
Scharfenberger-Schmeer	Maren	Dr.	DKFZ		Cancer Genome Comparisons
Pfeufer	Arne	PD Dr.	TU München		Cardiomyopathy Re-sequencing
Weichenhan	Dieter	PD Dr.	Universität Heidelberg		Cardiomyopathy Re-sequencing
Strom	Tim	Dr.	Helmholtzzentrum München		Coverage and variation detection

IA Whole Genome and Transcriptome Amplification in Large Biobanks

Koordination: Prof. Dr. Dr. H.-Erich Wichmann,
Dr. Christian Korfhage

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Teilprojekt Titel**
Korfhage	Christian	Dr.	Qiagen	1	Development and standardization of new WGA and WTA methods
Klopp	Norman	Dr.	HMGU	2	Provision of biosamples of different quality to test whole genome and transcriptome amplification techniques.
Wichmann	H.-Erich	Prof.Dr. Dr.	HMGU	3	Transfer of the results to international organisations in the field of biobanking

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