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Welcome Remarks

Dear conference participant,

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

4th Annual Meeting of NGFN-Plus and NGFN-Transfer
in the Program of Medical Genome Research
26th – 28th September 2011 at Urania, Berlin.

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

In honor of the **10th anniversary of the NGFN** – whose success is documented by more than 4,000 publications and 100 patent applications – we celebrate the "Tag der Genomforschung" in advance of this years' Meeting, on September 26th 2011. At this event for the general public, highlights of NGFN research are demonstrated in short talks and poster exhibition, a panel discussion will call the most current issues, and on-site experiments make human genome research accessible to all interested persons.

The **Annual Meeting** starts in direct succession of the "Tag der Genomforschung" on September 26 with the **Satellite Symposium** entitled *Next-Generation Sequencing.* The presentation of novel results by employing this powerful application will demonstrate impressive results in medical genome research.

In the main program on September 27 and 28, the **five symposia** entitled *Genomics of CNS Disorders, Genomics of Cardiac Disease and Metabolism, From Genomics to Application, Genomics of Infection, Inflammation & Environmental Interaction, and Genomics of Cancer* cover the enormous scientific spectrum of the NGFN. Internationally renowned keynote speakers will open each symposium with an overview lecture, followed by scientists of the NGFN presenting their latest results on selected topics.

To all five 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 2011" sponsored by Roche Diagnostics Deutschland GmbH. Annemarie Poustka made outstanding achievements in the field of Genome Research and was a visionary scientist for the NGFN.

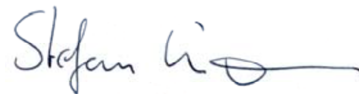
The **highlight Evening Lecture** on Tuesday evening will be given by Prof. Klaus Lindpaintner on *Future Medicine: The promise and challenge of translating science into health care.*

Company satellite lunch sessions round the program off and an industrial exposition offers comprehensive information on latest technology developments with relevance for researchers of the network.

Last but not least: don't miss the **get-together** with the scientific community in a relaxed ambience with good wine, tasty finger food and nice music!

To all members of NGFN-Plus and NGFN-Transfer, this is a great opportunity for meeting each other within the BMBF Program of Medical Genome Research, to find new collaborators and to reinforce existing co-operations. We are pleased to welcome many former members from 10 years of NGFN, all scientists who are interested in the program as well as all further visitors of our conference and invite for active participation in the scientific discussion and exchange.

Bonn and Heidelberg, September 14, 2011



Prof. Dr. Markus Nöthen

PD Dr. Stefan Wiemann

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

Conference Management

NGFN Geschäftsstelle
c/o Dt. Krebsforschungszentrum, DKFZ
Im Neuenheimer Feld 580, V025
D-69120 Heidelberg
Fax: +49 (0)6221 42 46 51

Dr. Silke Argo
Telefon: +49 (0)6221 42 47 43
E-Mail: s.argo@dkfz.de

Dr. Anke Bentmann
Telefon: +49 (0)6221 42 47 42
E-Mail: a.bentmann@dkfz.de

Dr. Tanja Jutzi
E-mail: t.jutzi@dkfz.de
Phone: +49-6221-424767

Dr. Johanna Lampert
E-mail: j.lampert@dkfz.de
Phone: +49-6221-424767

Anita Miehle
E-mail: a.miehle@dkfz.de
Phone: +49-6221-424649

Scientific Program Committee

Prof. Dr. Martin Hrabě de Angelis
Helmholtz Zentrum München

Prof. Dr. Joachim Jankowski
Charité Berlin

Prof. Dr. Hugo A. Katus
Universitätsklinik Heidelberg

Prof. Dr. Hans Lehrach
Max-Planck-Institut für Molekulare Genetik, Berlin

Prof. Dr. Peter Lichter
DKFZ Heidelberg

Prof. Dr. Markus Nöthen
Friedrich-Wilhelms Universität Bonn

Prof. Dr. Matthias Riemenschneider
Universität des Saarlandes

Prof. Dr. Stefan Schreiber
Universitätsklinikum Schleswig-Holstein,
Campus Kiel

Prof. Dr. Heribert Schunkert
Universitätsklinikum Schleswig-Holstein,
Campus Lübeck

Prof. Dr. H.-Erich Wichmann
Helmholtz Zentrum München

PD Dr. Stefan Wiemann
DKFZ Heidelberg

Prof. Dr. Wolfgang Wurst
Helmholtz Zentrum München

Program-at-a-glance

Monday, September 26th	
4.30 – 7.30 pm	**Satellite Symposium**: Next-Generation Sequencing (Org. Philip Rosenstiel)
7.30 pm	***Supper***

Tuesday, September 27th	
9.00 – 10.15 am	**Symposium I – Genomics of CNS Disorders** Julie Williams (Keynote) – Günter Höglinger – Aaron Voigt
10.15 – 10.45 am	**Coffee Break**
10.45 – 11.30 am	**Symposium I – Genomics of CNS Disorders** Sandra Meier – Hans-Hilger Ropers – Elisabeth Graf
11.30 – 1.30 pm **11.30 – 1.30 pm**	***Lunch Break and Poster Session I*** **Company Satellite Sessions** Roche Diagnostics Deutschland GmbH – chemagen Biopolymer-Technologie AG
1.30 – 2.00 pm	**Welcome:** **Stefan Wiemann**, Spokesperson for the Project Committee of NGFN-Plus / NGFN-Transfer in the Program of Medical Genome Research **Frank Laplace**, Federal Ministry of Education and Research, Germany
2.00 – 3.45	**Symposium II - Genomics of Cardiac Disease and Metabolism** Leif Groop (Keynote) – Christian Gieger – Nadja Knoll – Benjamin Meder – Thorsten Kessler
3.45 – 4.30 pm	**Coffee Break**
4.30 – 7.00 pm	**Symposium III – From Genomics to Application** Cornelia van Duijn (Keynote) – Christoph Bock – Angelika Daser – Hans Lehrach – Martin Hrabé de Angelis – Henk Stunnenberg (Keynote)
7.00 – 8.00 pm	**Evening Lecture:** Klaus Lindpaintner
8.00 – 10.00 pm	***Get-Together (Wine, Cheese, Music)***

Wednesday, September 28th	
9.00 - 10.45 am	**Symposium IV – Genomics of Infection, Inflammation & Environmental Interaction** Karin de Visser (Keynote) – Robert Häsler – Martin Kerick – Adam Baker – Stefan Wiemann
10.45 - 12.45 pm **10.45 - 12.45 pm**	***Lunch Break and Poster Session II*** **Company Satellite Sessions:** Complete Genomics – Life Technologies – Illumina
12.45 - 1.00 pm	**Ceremony: "Annemarie Poustka Poster Award of Medical Genome Research 2011" sponsored by Roche Diagnostics Deutschland GmbH**
1.00 - 1.45 pm	**Symposium V: Genomics of Cancer** Alessandro Prigione – Christian Wichmann – Ruprecht Kuner
1.45 - 2.15 pm	***Coffee Break***
2.15 - 3.30 pm	**Symposium V: Genomics of Cancer** Jörg Hoheisel – Alexandra Farrall – Ivo Gut (Keynote)
3.30 - 3.45 pm	**Concluding Remarks: Markus Nöthen**, Spokesperson for the Project Committee of NGFN-Plus / NGFN-Transfer in the Program of Medical Genome Research

Program

Monday, September 26, 2011	
4.30 – 7.30 pm	**Satellite Symposium**: Next-Generation Sequencing (Org. Philip Rosenstiel)
4.30 – 5.00 pm	**Election Project Committee** (by invitation only)
7.30 pm	***Supper***

Tuesday, September 27, 2011	
Symposium I:	**Genomics of CNS Disorders**
9.00 – 9.45 am	**Keynote: Julie Williams,** Cardiff University School of Medicine, Cardiff, UK *Defining the Genetic Architecture of Alzheimer's Disease*
9.45 – 10.00 am	**Günter Höglinger**, Philipps-University Marburg, Germany *Identification of common variants influencing risk of the tauopathy Progressive Supranuclear Palsy*
10.00 – 10.15 am	**Aaron Voigt**, University Medical Center, RWTH Aachen, Germany *The Mitochondrial Chaperone Protein TRAP1 Mitigates α-Synuclein Toxicity*
10.15 – 10.45 am	***Coffee Break***
10.45 – 11.00 am	**Sandra Meier**, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany *Association between negative mood delusions in bipolar disorder and genetic variations in 3q26.1*
11.00 – 11.15 am	**Hans-Hilger Ropers**, Max Planck Institute for Molecular Genetics, Berlin, Germany *Deep sequencing reveals 50 novel genes for recessive cognitive disorders*
11.15 – 11.30 am	**Elisabeth Graf**, Helmholtz Zentrum Munich, Neuherberg, Germany *Exome Sequencing Reveals a Mutation in the Retromer Protein VPS35 as Cause for Late-Onset Parkinson's Disease*
11.30 – 1.30 pm	***Lunch Break and Poster Session I***
11.30 – 1.30 pm	**Company Satellite Sessions**
11.45 – 12.15 pm	**Roche Diagnostics Deutschland GmbH** **Bernd Timmermann**, Head Next Generation Core Facility, MPI MG Berlin *Benefits of 454 Sequencing in Genome Analysis*
12.25 – 12.55 pm	**chemagen Biopolymer-Technologie AG** **Cecilia Agardh**, Karolinska Institutet Biobank, Stockholm Sweden *New processes for large scale DNA extractions at Karolinska Institutet Biobank*

Welcome	
1.30 – 2.00 pm	**Stefan Wiemann**, German Cancer Research Center (DKFZ) Heidelberg, Spokesperson for the Project Committee of NGFN-Plus / NGFN-Transfer in the Program of Medical Genome Research **Frank Laplace**, Federal Ministry of Education and Research, Germany

Symposium II:	**Genomics of Cardiac Disease and Metabolism**
2.00 – 2.45 pm	**Keynote: Leif Groop**, Lund University, Malmö, Sweden *Genetics of type 2 diabetes- quo vadis?*
2.45 – 3.00 pm	**Christian Gieger**, Helmholtz Zentrum Munich, Germany *Human metabolic individuality in biomedical and pharmaceutical research*
3.00 – 3.15 pm	**Nadja Knoll**, University of Duisburg-Essen, Essen, Germany *Gene set of nuclear encoded mitochondrial regulators is enriched for inherited variation in obesity*
3.15 – 3.30 pm	**Benjamin Meder**, University Hospital Heidelberg, Germany *Genome-wide association study identifies novel risk locus for dilated cardiomyopathy*
3.30 – 3.45 pm	**Thorsten Kessler**, University of Lübeck, Germany *Investigation of the coronary artery disease risk gene ADAMTS-7 in a murine knockout-model*
3.45 – 4.30 pm	***Coffee Break***

Symposium III:	**From Genomics to Application**
4.30 – 5.15 pm	**Keynote: Cornelia van Duijn**, Erasmus Medical Center, Rotterdam, Netherlands *From Genetic Research to Clinical Translation*
5.15 – 5.30 pm	**Christoph Bock**, Broad Institute, Cambridge, MA, USA *A functional genomics scorecard predicts the quality and utility of human pluripotent cell lines for regenerative medicine*
5.30 – 5.45 pm	**Angelika Daser**, Fertility Center Wiesbaden, Germany *High throughput copy number counting in single cells – a method for the detection of meiotic and mitotic errors*
5.45 – 6.00 pm	**Hans Lehrach**, MPI for Molecular Genetics, Berlin, Germany *The IT Future of Medicine – a flagship initiative to revolutionize our health care system*
6.00 – 6.15 pm	**Martin Hrabé de Angelis**, Helmholtz Zentrum Munich, Germany *Next steps in systemic analysis of mouse mutants at the German Mouse Clinic*
6.15 – 7.00 pm	**Keynote: Henk Stunnenberg,** Nijmegen Centre for Molecular Life Sciences, Nijmegen, Netherlands *The BLUEPRINT of hematopoiesis*

Evening Lecture:

7.00 – 8.00 pm	**Klaus Lindpaintner,** SDIX (Strategic Diagnostics Inc.), Newark, Delaware, USA *Future Medicine: The promise and challenge of translating science into health care*
8.00 – 10.00 pm	***Get-Together (Wine, Cheese, Music)***

Wednesday, September 28, 2011

Symposium IV: Genomics of Infection, Inflammation & Environmental Interaction

9.00 – 9.45 am	**Keynote: Karin de Visser,** The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands *Impact of the immune system on metastatic breast cancer and chemotherapy efficacy*
9.45 – 10.00 am	**Robert Häsler**, Christian-Albrechts University Kiel, Germany *Impaired host-microbiome crosstalk in inflammatory bowel disease*
10.00 – 10.15 am	**Martin Kerick**, MPI for Molecular Genetics, Berlin, Germany *Integrative data analysis of cancer tissues using next generation sequencing*
10.15 – 10.30 am	**Adam Baker**, Exiqon A/S, Vedbaek, Denmark *Early detection of colorectal cancer from patient blood plasma using microRNA-based RT-qPCR*
10.30 – 10.45 am	**Stefan Wiemann**, DKFZ Heidelberg, Germany *IG Cellular Systems Genomics: Network analysis of tumor drug resistance*
10.45 – 12.45 pm	***Lunch Break and Poster Session II***

10.45 – 12.45 pm Company Satellite Sessions:

11.00 – 11.30 am	**Stephen E. Lincoln**, **Complete Genomics**, Inc. Mountain View, California USA *Genome-Wide Detection and Analysis of Germline and Somatic Variations in Tumors*
11.35 – 12.05 pm	**Goran Tomicic, Life Technologies Corporation** *Ion Torrent PGM™ for Clinical Genetics*
12.10 – 12.40 pm	**Neil Ward**, Sequencing Specialist – EMEA, **Illumina** *Illumina Sequencing - Whole genomes to amplicons*

12.45 – 1.00 pm Poster Award Ceremony:

12.45 – 1.00 pm	**Ceremony: "Annemarie Poustka Poster Award of Medical Genome Research 2011"** sponsored by Roche Diagnostics GmbH

Symposium V:	Genomics of Cancer
1.00 – 1.15 pm	**Alessandro Prigione**, MPI for Molecular Genetics, Berlin, Germany *Human Induced Pluripotent Stem Cells Harbor Homoplasmic and Heteroplasmic Mitochondrial DNA Mutations While Maintaining Human Embryonic Stem Cell-like Metabolic Reprogramming*
1.15 – 1.30 pm	**Christian Wichmann**, Institute for Biomedical Research, Frankfurt am Main, Germany *Development of molecular inhibitors targeting hot spots of AML1/ETO dimer-tetramer transition*
1.30 – 1.45 pm	**Ruprecht Kuner**, DKFZ & NCT, Heidelberg, Germany *miRNAs in prostate cancer*
1.45 – 2.15 pm	***Coffee Break***
2.15 – 2.30 pm	**Jörg Hoheisel**, DKFZ Heidelberg, Germany *Affinity-based proteomic analysis of pancreatic cancer*
2.30 – 2.45 pm	**Alexandra Farrall**, MPI for Molecular Genetics, Berlin, Germany *Multiple (epi)genetic modifier loci of Apcmin-induced tumourigenesis identified using chromosome substitution strains*
2.45 – 3.30 pm	**Keynote: Ivo Gut,** Centro Nacional de Análisis Genómico, Barcelona, Spain *Cancer Genome Analysis in Chronic Lymphocytic Leukemia*
3.30 – 3.45 pm	**Concluding Remarks: Markus Nöthen**, Friedrich-Wilhelms University, Bonn, Spokesperson for the Project Committee of NGFN-Plus / NGFN-Transfer in the Program of Medical Genome Research
4.00 – 5.00 pm	**Constitutive Meeting of the Project Committee** (members only)

Satellite Symposium

4th Annual Meeting of NGFN-Plus and NGFN-Transfer in the Program of Medical Genome Research

Urania, Berlin

Satellite Symposium „Next Generation Sequencing“

September 26, 2011

Scientific Organization: **Philip Rosenstiel, Institute of Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany**

4.30-4.40 pm	**Welcome and Introduction:** Philip Rosenstiel
Session I	
4.40-5.00 pm	**Joris Veltman (UMC St Radboud, Nijmegen)** Identifying de novo mutations from complex NGS data sets
5.00-05.20 pm	**Christoph Bock (Broad Institute and Max Planck Institute for Informatics)** Performing epigenome-wide association studies (EWAS) and biomarker discovery using next-generation sequencing
5.20-5.40 pm	**Lars Dölken (Divison of Virology, Department of Medicine, at Addenbrooke's Hospital, Cambridge**) Ultra short and progressive 4sU-tagging reveals key characteristics of RNA processing at nucleotide resolution
5.40-6.00 pm	***Coffee Break***
Session II	
6.00-6.20 pm	**Marie-Laure Yaspo (Max Planck Institute for Molecular Genetics, Berlin)** New Horizons in Cancer Genetics using Next Generation Sequencing
6.20-6.40 pm	**Stefan Haas (Max-Planck Institute for Molecular Genetics, Berlin)** Detection of disease-causing mutations in patients with X-linked intellectual disability (XLID)
6.40-7.00 pm	**Marc Zapatka (German Cancer Research Center, Heidelberg)** After the first personal cancer genomes – where do we go?

Session II	
7.00-7.20 pm	**Peer Bork (European Molecular Biology Laboratory EMBL, Heidelberg)** Identification of functional and phylogenetic signals in gut metagenomes
7.20-7.30 pm	Concluding remarks
7.30 pm	***Supper***

Satellite Symposium Abstracts

Next-Generation Sequencing

NGS-based detection of de novo mutations in intellectual disability

Presenting Author: Joris A Veltman

Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, NL

Humans have an exceptionally high per-generation mutation rate of 7.6×10^{-9} to 2.2×10^{-8}. These spontaneous germline mutations can have serious phenotypic consequences when affecting functionally relevant bases in the genome. These mutations could in fact explain a major paradox in the evolutionary genetic theory of neurodevelopmental disorders like intellectual disability, autism and schizophrenia that are associated with a severely reduced fecundity but remain frequent in the human population. The detection of these mutations has been complicated for a long time because (1) these mutations can occur all over the genome, (2) the mutations are expected to be rare and the recurrence rate will be low in the disease population, (3) and no families are available as the diseases are associated with reduced fecundity. The role of these mutations is therefore unknown and approaches are needed that can comprehensively and reliably detect these mutations in individual patients.
In this presentation, I will describe our recent work on using a family-based exome sequencing approach to test this de novo mutation hypothesis in 10 patients with unexplained intellectual disability[1]. Unique non-synonymous de novo mutations were identified and validated in nine genes. Six of these, identified in different patients, were likely pathogenic based on gene function, evolutionary conservation and mutation impact. These findings, when replicated, provide a strong experimental support for a de novo paradigm for intellectual disability. In my presentation I will also discuss related work in autism[2] and schizophrenia[3,4].

References:

1. Vissers et al. A de novo paradigm for mental retardation. Nat Genet 42: 1109-12 (2010).

2. O'Roak et al. Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. Nat Genet 43: 585-9 (2011).

3. Girard et al. Increased exonic de novo mutation rate in individuals with schizophrenia. Nat Genet, online.

4. Xu et al. Exome sequencing supports a de novo mutational paradigm for schizophrenia. Nat Genet, online.

Performing epigenome-wide association studies (EWAS) and biomarker discovery using next-generation sequencing

Presenting Author: Christoph Bock

Broad Institute, Cambridge, USA and Max Planck Institute for Informatics, Saarbrücken

Epigenome mapping has played an important role in establishing the prevalence of altered DNA methylation in cancer cells; and it is increasingly applied to investi-gate diseases other than cancer. Indeed, epigenetic events could provide a tractable link between the genome and the environment, with the epigenome emerging as a biochemical record of relevant life events.
Systematic investigation of these topics requires powerful, accurate and cost-efficient methods for epigenome profiling of human samples. We have recently benchmarked four methods for genome-wide DNA methylation mapping in terms of their accuracy and power to detect DNA methylation differences (Bock et al. 2010 Nat Biotechnol). This technology comparison was designed to mimic the setup of a typical EWAS, suggesting that our bioinformatic and experimental approach could provide a blueprint for designing and executing large-scale EWAS investigating the epigenetic basis of human diseases. Furthermore, we have devel-oped bioinformatic tools for epigenetic biomarker development, which facilitate the adaptation of disease-specific epigenetic alternations for clinical diagnostics.
My talk will discuss this ongoing work and highlight practical implications for conducting epigenome association studies and performing epigenetic biomarker development.

The described work was in part funded by NIH grant U01ES017155 (Roadmap Epigenome Mapping Center) and the Broad Institute’s Epigenome Initiative.

Ultra short and progressive 4sU-tagging reveals key characteristics of RNA processing at nucleotide resolution

Presenting Author: Lars Dölken

University of Cambridge, Department of Medicine, Addenbrooke's Hospital, Cambridge, UK

The rates of transcription, RNA processing and decay determine cellular RNA levels. Metabolic tagging of newly transcribed RNA using 4-thiouridine can distinguish the contribution of RNA synthesis and decay. However, the kinetics of RNA processing so far remained unresolved.
We combined ultra-short and progressive 4sU-tagging with RNA-seq. This not only provides snap-shot pictures of mammalian gene expression but reveals distinct characteristics of RNA processing at nucleotide resolution. In this way, we identified distinct classes of splicing kinetics including rapid co-transcriptional processing, intron retention and reduced processing rates of introns encoding snoRNAs. Interestingly, degradation rate correlated with intron length and transcripts containing retained introns were found to be efficiently degraded later on or subjected to secondary splicing events. Furthermore, marked differences in the processing efficiency of many non-coding RNAs were revealed. As such processing of most human snoRNAs was found to be surprisingly inefficient offering great potential for regulation. In contrast, highly efficient processing was characteristic of the snoRNAs of the imprinted SNORD116 cluster. In summary, this study provides the tools and highlights the need to closely study the contribution of RNA processing in the regulation of gene expression.

New Horizons in Cancer Genetics using Next Generation Sequencing

Presenting Author: Marie-Laure Yaspo

Max Planck Institute for Molecular Genetics, Berlin

We are currently using next generation sequencing as partners of several consortia in cancer research: ICGC (International Cancer Genome Consortium) PedBrain-medulloblastoma, ICGC prostate cancer, TREAT 20 melanoma and ONCOtrack colon cancer. The sequences of the genomes of tumor and blood control samples are sequenced at a depth of ca. 30x .
Simultaneously to the identification of the somatic DNA variants, high-definition transcriptome landscapes are obtained with RNAseq, detecting altered gene activities. Data analysis of heterogeneous tumor samples poses a number of challenges, due to the aneuploidy of cancer cells and to the contamination with surrounding tissue. Focusing on the TREAT20 melanoma project, a translational medicine cooperation effort with the Charite Comprehensive Cancer Center, we will show how the digital sequencing information can be exploited for charting molecular and biological pathways associated to cancerogenesis.

Detection of disease-causing mutations in patients with X-linked intellectual disability (XLID)

Presenting Author: Stefan Haas

Max-Planck Institute for Molecular Genetics, Berlin

Next Generation Sequencing is an efficient mean to screen large cohorts patients for potential disease-causing mutations. The steadily increasing throughput as well as the application of barcoding techniques allows to analyze hundreds of patients within a relatively short time frame. Here we present the experiences made when analyzing NGS data related to ~300 patients suffering of X-linked intellectual disability (XLID). Advantages and limitations of NGS will be discussed particulary in regard to the diagnostic potential.

After the first personal cancer genomes – where do we go?

Presenting Author: Marc Zapatka

Division of Molecular Genetics, German Cancer Research Center, Heidelberg, Germany

Cancer is a highly complex and versatile disease of the genome. A key milestone was passed with the publishing of the first complete whole genome of a human cancer and its paired normal genome. Due to the falling costs of sequencing we will likely approach an era in which access to personalized genomic information is widely spread. The time from the discovery of driver mutations to first clinical tests and the approval of new drugs is shortened. However bridging the gap between the genome sequence information and medicine is far from being solved. To facilitate the transfer of discovery science to medicine a solid understanding of the mechanism of driver genes is needed to enable a conversion of the genomic discovery to a clinically applicable therapeutic or diagnostic endpoint. This is a real challenge due to the interaction and interdependence of genetic, epigenetic and transcriptomic events. Finally in the future we might treat patients as individuals based on their genetically defined actionable mutation profile and thereby improving the lives of many patients with cancer.

Identification of functional and phylogenetic signals in gut metagenomes

Presenting Author: Peer Bork

EMBL, Heidelberg

Although application of modern sequencing technologies to environmental sequencing [1] enables a wealth of metagenomics data, our understanding of microbial community functioning remains limited, both in terms of internal interactions and its adaptation to environmental properties and changes. Using a variety of newly developed tools such as the metagenomics pipeline, SMASH [2], we analyzed stool samples from individuals from 6 countries and identified three preferred community compositions, dubbed enterotypes [3]. These are driven by networks of interacting genera and seem to be independent of a number of host properties studied such as nationality, age, gender or body mass index. However, we did find genes or pathways that correlate well with each of the latter properties. Thus, there is hope to establish diagnostic, perhaps even prognostic molecular markers for complex human properties such as diseases. To gain insight into the evolution of the microbial gut communities we analyzed the variation landscape in samples from more than 100 individuals, each of these appear to carry specific mutation patterns.

1. Qin et al., Nature. 2010, 464, 59-65
2. Arumugam, M. et al., Bioinformatics 2010, 26,2977-2978
3. Arumugam, M. et al. Nature. 2011, 473, 174-180.

Main Program

Main Program

27th to 28th September 2011

Program (with speakers' biosketch)

Tuesday, September 27th, 2011

Symposium I: Genomics of CNS Disorders

9.00 – 9.45 am

Keynote Presentation

Defining the Genetic Architecture of Alzheimer's Disease

Julie Williams

Julie Williams has made a significant contribution to the field of Alzheimer's disease genetics. Her publication in 2009 (Harold et al., Nature Genetics) of the first new susceptibility genes for 17 years defined a pivotal moment in Alzheimer's research (AD). Since then she has continued the momentum and has just completed powerful genome-wide studies, with her group discovering 8 of the 9, new susceptibility loci identified in the last two years. There are now 10 known susceptibility genes for AD. Early in her career she understood the complexity of AD genetics and began focussing her research on large powerful studies. Twelve years ago JW changed her strategy to focus on collecting case-control samples, well before others in the field. This put her group in a strong position when technological development made large scale genome-wide studies feasible, forming a major collaboration on genetic association across countries. Her work has since received extensive support in the literature with findings replicated in numerous samples. What is most striking about her groups work is that the genes identified show patterns of relationship which implicate new disease pathways.

In 2008 she became Chief Scientific Advisor to the Alzheimer's Research Trust. She has used this position to broaden the funding options available to scientists, increase research capacity and training in the area and to keep the importance of dementia research on the National agenda. She has also advised UK and Welsh Governments on dementia policy.

9.45 – 10.00 am

Identification of common variants influencing risk of the tauopathy Progressive Supranuclear Palsy

Günter Höglinger

Prof. Dr. med. **Günter U. Höglinger** studied Physics and Medicine at the Universities of Regensburg and Würzburg. His thesis work was done at the Universities of Munich and Berne. A 3-years postdoctoral period was done at an INSERM Unit in Paris. Thereafter, he started a junior research group at the University of Marburg. His scientific work is focused on the pathogenesis and therapy of Parkinson Syndromes, ranging from molecular, cellular and animal models to clinical trials in patients. Since 2011, Prof. Höglinger holds a DFG-funded W3 Heisenberg Professorship for Translational Neurodegeneration Research at the German Center for Neurodegenerative Diseases and the Technical University Munich.

10.00 – 10.15 am ***The Mitochondrial Chaperone Protein TRAP1 Mitigates α-Synuclein Toxicity***

Aaron Voigt

1993-98	Study of biology, Georg-August-Universität, Göttingen, Germany
1998	Diploma thesis, Dep. of Biochemistry, Prof. Dr. Kurt von Figura, Georg-August-Universität, Göttingen, Germany
1999-2005	Ph.D. thesis , Dep. of Molecular Developmental Biology, Prof. Dr. Herbert Jäckle, Max-Planck Institute for Biophysical Chemistry, Göttingen, Germany
2005-2009	Postdoctoral research associate, Dep. of Neurodegeneration and Restorative Research , Prof. Jörg B. Schulz, Georg-August-Universität, Göttingen, Germany
Since 2009	Group leader “Neurodegeneration in *Drosophila*”, Dep. of Neurology, Prof. Jörg B. Schulz, University Medical Center RWTH, Aachen, Germany

Research interest: Developmental biology, nervous system development, *Drosophila* models of human neurodegenerative diseases, neuronal cell death mechanisms, gene therapy and other experimental therapeutics, molecular mechanisms and cellular pathways in neurodegeneration.

10.15 – 10.45 am ***Coffee Break***

10.45 – 11.00 am ***Association between negative mood delusions in bipolar disorder and genetic variations in 3q26.1***

Sandra Meier

Sandra Meier holds a MSc in Clinical Psychology, Psychotherapy and Psychopathology psychology from the Unversity of Basel, Switzerland. She enrolled at the Central Institute of Mental Health, Mannheim 2008 and is currently completing her PhD at the Department of Genetic Epidemiology in Psychiatry, under supervision of Prof. Marcella Rietschel.

Her work focuses on elucidating the genetic underpinnings of symptom dimensions in psychiatric disorders using single-marker analyses and genome-wide association scans.

11.00 – 11.15 am *Deep sequencing reveals 50 novel genes for recessive cognitive disorders*

Hans-Hilger Ropers

Forschungsschwerpunkte/Projekte: Genetische Ursachen monogen vererbter Krankheiten, speziell genetisch bedingter Formen der geistigen Behinderung; Next-Generation-Sequencing; Publikationen: 350
Vita: geb. 1943, Medizinstudium Uni Freiburg und TU München 1965-70, Prom. Uni Freiburg 1972, Habil. Humangenetik Uni Freiburg 1978, wiss. Mitarbeiter und Ass. Prof. Uni Freiburg 1971-84, Apl. Prof. Uni Freiburg 1981, Ord. und Leiter Dept. of Human Genetics, Univ. of Nijmegen (NL), Facharzt für Klinische Genetik 1987, seit 1994 Direktor am MPI für molekulare Genetik, Berlin. Mitgl. Royal Netherlands Academy of Arts and Sciences (seit 2002); Council Member HUGO (2003-2010); Mitgl. BBAW seit 2003, Sekretar Kl. BioMed BBAW seit 2008; Ehrenmitgl. Ges. f. Humangenetik seit 2009.

11.15 – 11.30 am *Exome Sequencing Reveals a Mutation in the Retromer Protein VPS35 as Cause for Late-Onset Parkinson's Disease*

Elisabeth Graf

I studied Biology at the University Greifswald and graduated 2009 in human genetics. Currently, I am a third year PhD student at the Helmholtz Zentrum Munich in the Department of Human Genetics. The main focus of my work is the identification of causative variants of rare heritable diseases via whole exome sequencing.
Additionally, we are performing trio-based exome sequencing to identify de novo mutations in sporadic cases of several disorders. Recently, I established an automated library preparation workflow to generate whole genome and whole exome libraries for next generation sequencing.

11.30 – 1.30 pm *Lunch Break and Poster Session I*
(11.30 – 12.30 pm odd numbers, 12.30 – 1.30 pm even numbers)

11.30 – 1.30 pm **Company Satellite Sessions**

11.45 – 12.15 pm **Roche Diagnostics Deutschland GmbH**
Bernd Timmermann, Head Next Generation Core Facility, MPI MG Berlin
Benefits of 454 Sequencing in Genome Analysis

12.25 – 12.55 pm **chemagen Biopolymer-Technologie AG**
Cecilia Agardh, Karolinska Institutet Biobank, Stockholm Sweden
New processes for large scale DNA extractions at Karolinska Institutet Biobank

Welcome

1.30 – 2.00 pm

Stefan Wiemann, German Cancer Research Center (DKFZ) Heidelberg, Speaker Project Committee of NGFN-Plus / NGFN-Transfer in the Program of Medical Genome Research

Frank Laplace, Federal Ministry of Education and Research, Germany

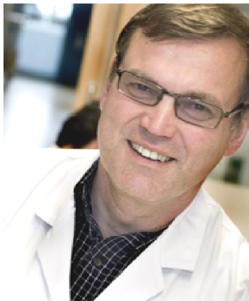
Symposium II: Genomics of Cardiac Disease and Metabolism

2.00 – 2.45 pm

Keynote Presentation

Genetics of type 2 diabetes - quo vadis?

Leif Groop



Leif Groop, M.D., Ph.D. is since 1993 Professor in Endocrinology at Lund University and Director of Lund University Diabetes Centre.
He received his MD at University of Berne, Switzerland and PhD at University of Helsinki, Finland. After a PostDoc period at Yale University he devoted his research to dissection of the heterogeneity of diabetes but also to explore the pathogenic events leading to type 2 diabetes. As an important tool to achieve this goal, he initiated the Botnia Study at the west coast of Finland, one of the world's largest family studies on type 2 diabetes. This has been an invaluable tool in dissecting the phenotypic and genotypic heterogeneity of type 2 diabetes. The research group has been involved in many of the genetic discoveries on type 2 diabetes during the past 15 years, including one of the first whole genome association studies for type 2 diabetes. He has served on numerous editorial boards and achieved several international recognitions, including the Jacob Poulsen, Knud Lundbaek and the Claude Bernard awards.

2.45 – 3.00 pm

Human metabolic individuality in biomedical and pharmaceutical research

Christian Gieger

Christian Gieger studied Statistics at the Ludwig-Maximilians-Universität München where he received his PhD in 1998. Between 1993 and 1998 he worked as research associate at the Institute of Statistics, Ludwig-Maximilians-Universität München and between 1995 and 1999 also at the Collaborative Research Center SFB 386. From 1999 to 2002 he worked in the industry for IBM and LION bioscience, Heidelberg and from 2002 to 2004 as scientist at the Fraunhofer Institute for Algorithms and Scientific Computing, Sankt Augustin. From 2004 to 2010 he worked as scientist at the Institute of Epidemiology of the Helmholtz Zentrum München. From 2009 to 2010 he acted as Head of the Research Group 'Genetic Epidemiology' at the Institute of Epidemiology. In 2011 his research group moved into the newly founded Institute of Genetic Epidemiology at the Helmholtz Zentrum München. He published on genome-wide association studies for various traits related to metabolic and cardiovascular diseases. His particular interest is focused on the genetics of intermediate risk factors and metabolic profiles (Metabolomics).

3.00 – 3.15 pm

Gene set of nuclear encoded mitochondrial regulators is enriched for inherited variation in obesity

Nadja Knoll

Nadja Knoll is a Ph.D. student at the Department of Child and Adolescent Psychiatry, University of Duisburg-Essen. She joined the group of Prof. Dr. Johannes Hebebrand and PD Dr. Anke Hinney in July 2010. Her research topic deals with genetic mechanisms in early onset obesity. She is particularly interested in the involvement of mitochondrial genes/gene variants and their association with body weight.

Nadja Knoll studied Nutritional Sciences at the Friedrich-Schiller-University of Jena. Her master thesis on the "Assessment of the Dietary Composition in a Maasai Community (Kajiado District, Kenya) with Focus on Iron and Fatty Acid Supply" was performed at Department of Nutritional Physiology, Institute of Nutrition, FSU Jena (Prof. Jahreis) and at the Jomo Kenyatta University Juja/Nairobi (Kenya). The stay abroad was funded by the DAAD.

3.15 – 3.30 pm

Genome-wide association study identifies novel risk locus for dilated cardiomyopathy

Benjamin Meder

Benjamin Meder 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. 2009-2011 he was awarded with the Research fellowship "Young Investigator Award" of the Medical Faculty of Heidelberg, 2009 with the Best Poster Award, 7th Dutch-German Meeting of the Molecular Cardiology Groups and 2010 with the Wilhelm P. Winterstein Science Award of the German Heart Foundation.

From 2005 - 2009 Benjamin Meder was postdoctoral research fellow in the group of Prof. Wolfgang Rottbauer at the University of Heidelberg and since 2008 he is Head of the Laboratory of Molecular Genetics (NGFN Funding) in the Department of Internal Medicine III at the University Hospital of Heidelberg. He is elected coordinator of the Innovation Alliance "Subgenome Fractionation for High-throughput Sequencing" (NGFN Funding).

Research Interest: Translational biotechnology for the identification of novel biomarkers for cardiovascular diseases, development of novel gene diagnostic tools based on next-generation sequencing technology, dissection of the functional relevance of genetic and epigenetic alterations in the zebrafish model.

Memberships: Deutsche Gesellschaft für Kardiologie - Herz- und Kreislauf-forschung e.V., DGK working group 8 „Genetik und Molekularbiologie kardiovaskulärer Erkrankungen"

3.30 – 3.45 pm

Investigation of the coronary artery disease risk gene ADAMTS-7 in a murine knockout-model

Thorsten Kessler

Thorsten Kessler, born in 1984, is a postdoctoral fellow in the research group "Cardiovascular Molecular Genetics" (Head: Prof. Dr. Jeanette Erdmann) at the University of Lübeck. He focusses on the involvement of ADAMTS-7 in the pathophysiology of atherosclerosis. Besides functional studies in atherosclerosis animal models, he is interested in downstream signaling mechanisms and pharmacological therapeutic approaches.
He studied medicine at the Saarland University and the Technical University of Munich and finished his MD thesis in 2010 at the Institute of Experimental and Clinical Pharmacology and Toxicology (Saarland University). After finishing medical school, he worked as a postdoctoral fellow at the Institute of Pharmacology and Toxicology at the Technical University of Munich. In 2011 he started his residency training at the Medizinische Klinik II (Director: Prof. Dr. Heribert Schunkert) at the University of Lübeck and joined the working group "Cardiovascular Molecular Genetics".

3.45 – 4.30 pm

Coffee Break

Symposium III: From Genomics to Application

4.30 – 5.15 pm

<u>Keynote Presentation</u>

From Genetic Research to Clinical Translation

Cornelia van Duijn

Cornelia van Duijn received her PhD in genetic epidemiology from the Erasmus University Rotterdam in 1991. Since 2001 she is a full professor of Genetic Epidemiology at the Department of Epidemiology of the Erasmus University Medical Center. She led genetic-epidemiological linkage and association studies of various complex disorders including Alzheimer's disease, Parkinson’s disease, open angle glaucoma, blood pressure and lipid metabolism. She has published over 575 scientific papers and has graduated 40 PhD students. Cornelia van Duijn is involved as a principle investigator in three large-scale population- and family-based studies. She heads the Erasmus Rucphen Family (ERF) study of 2500 relatives who go back to 30 closely related (first and second degree) founding couples. As a principal investigator she is responsible for the biobanking and genetic epidemiologic research of the Rotterdam study, a population-based study of 12,000 subjects age 55 years and older who have been followed over 18 years. Also in Generation R, a prospective cohort study from fetal life until young adulthood including 8000 children and their parents, she is responsible for the genetic epidemiologic research program. She is a leader in several international genome wide association consortia including CHARGE (Cohorts for Heart & Aging Research in Genome Epidemiology, ENGAGE (European Network for Genetic and Genomic Epidemiology), and EAGLE (Early Genetics and Life course Epidemiology). Over the years, she served on various scientific committees, including the International Society for Genetic

Epidemiology (IGES), the European Society for Human Genetics (ESHG) and the Molecular Epidemiology Group. She initiated an international education and training in genetic epidemiology. This program developed into the MSc and PhD program in Genetic Epidemiology of the Erasmus University Medical Center of which she is the scientific director. More than 200 (inter)national students finalized the MSc and PhD genetic epidemiology programs in the past 17 years.

5.15 – 5.30 pm

A functional genomics scorecard predicts the quality and utility of human pluripotent cell lines for regenerative medicine

Christoph Bock

Christoph Bock obtained a PhD in bioinformatics from the Max Planck Institute for Informatics and Saarland University. He subsequently joined the Broad Institute of MIT and Harvard as a postdoctoral researcher, contributing to the Roadmap Epigenomics Project. In parallel, Christoph leads a research group on computational epigenetics at the Max Planck Institute for Informatics. His recent publications include papers in Cell, Nature Biotechnology, Nature Methods, Genome Research, Genome Biology, PLoS Computational Biology and Bioinformatics. He has been appointed a Principal Investigator at Vienna's CeMM institute and Guest Professor at the Medical University of Vienna, starting in January 2011.

5.30 – 5.45 pm

High throughput copy number counting in single cells – a method for the detection of meiotic and mitotic errors

Angelika Daser

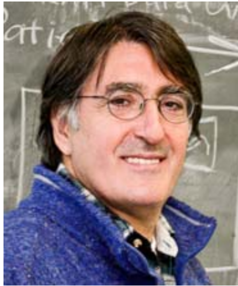
Present: Senior Scientist at the SH-Gen Forschungsgesellschaft bR, Wiesbaden; Topic: Development of novel techniques to improve pregnancy outcomes after ART

Past:
Medical School at the Free University Berlin; MD Thesis at the Max-Planck-Institute for Molecular Genetics, Berlin; Title: Monoclonal Antibodies against RNP- and Sm-Autoantigens
Postdoctoral Scientist at the Deutsche Rheumaforschungszentrum Berlin; Topic: Antigen Presentation and Immunodeviation
Phoenix Pharmacy Award for the work on Rational design of nonnatural peptides as high-affinity ligands for the HLA-B*2705 human leukocyte antigen
Postdoctoral Scientist at the Institute of Clinical Chemistry and Pathobiochemistry, Charite,Humboldt University, Berlin; Topic: Genetics of Atopy in Mouse Models
Habilitation in Pathobiochemistry at the Charite, Humboldt University, Berlin; Title: Cellular and genetic mechanisms of immunoregulation and –modulation
Postdoctoral Scientist at the Laboratory of Molecular Biology, Cambridge, U.K.; Topics: Genomics and genetics of solid tumours; mouse models of leukaemias and solid tumours

5.45 – 6.00 pm

The IT Future of Medicine – a flagship initiative to revolutionize our health care system

Hans Lehrach



Hans Lehrach studied Chemistry at the University of Vienna and accomplished his Ph.D. in 1974 at the MPI for Experimental Medicine and at the MPI for Biophysical Chemistry in Göttingen. He was a research fellow at Harvard University, Boston. After his return to Europe he took up position as the head of a research group at the EMBL, Heidelberg, and later on as head of the Department of Genome Analysis at the ICRF, London. In 1994, Hans Lehrach took up the post of Director at the Max Planck Institute for Molecular Genetics in Berlin and heads the Department of Vertebrate Genomics. At the same time he holds a Professorship at the faculty of Biochemistry at the Free University.

Hans Lehrach was a speaker of the German Human Genome Project and is currently a member of the project committee of the National Genome Research Network (NGFN). Moreover, he is e.g. a member of the European Molecular Biology Organization (EMBO) and of the scientific advisory board of the Austrian Genome Research Project (GENAU), as well as of Editorial boards of several scientific journals.

In 1993 Hans Lehrach was a Fellow of the American Association for the Advancement of Science, he received the Ján Jessenius SAS Medal of Honour for outstanding achievements in medical sciences of the Slovak Academy of Sciences (2003, Bratislava) and the Karl Heinz Beckurts Award for achievements in genome research (2004, Munich).

6.00 – 6.15 pm

Next steps in systemic analysis of mouse mutants at the German Mouse Clinic

Martin Hrabě de Angelis

Prof. Dr. **Martin Hrabě de Angelis** studied biology at the Philipps University in Marburg and received his PhD in 1994. He worked as postdoctoral fellow from 94 - 97 at the Jackson Laboratory in Bar Harbor/USA studying the Delta/Notch pathway and mouse mutant lines with impaired somitogenesis. In 2000 he was recruited as director of the Institute of Experimental Genetics at the Helmholtz Zentrum München (formerly GSF). He serves as full professor and chair of Experimental Genetics at the Technical University Munich. Hrabě de Angelis is director of the European Mouse Mutant Archive in Monterotondo/Rome Italy. In 2001 he founded the German Mouse Clinic (GMC) for systemic analysis of human diseases. He is member of the project committee of the national Genome Network (NGFN). Moreover, he is one of the founding members and part of the steering committee of the German Center for Diabetes Research DZD e.V. which has been established in 2009. His focus is in the fields of functional genetics and metabolic diseases. Hrabě de Angelis serves on a number of editorial boards and is author of more than 200 scientific publications.

6.15 – 7.00 pm

Keynote Presentation

The BLUEPRINT of hematopoiesis

Henk Stunnenberg

In 1996, **Hendrik G. Stunnenberg** was appointed full professor and head of the Department of Molecular Biology, and has an appointment at the Science and Medical Faculties, Radboud University Nijmegen, The Netherlands. He was a group leader at the EMBL Heidelberg, Germany in the Gene Expression program from 1985 to 1996, where he studied the action of nuclear receptors and also contributed very significantly to deciphering basal transcription processes. He is a member of EMBO since 1992. He is the founder and main organizer of the biennial EMBL meeting on transcription. His group was amongst the first in Europe to establish ChIP in combination with next generation sequencing platform.
His research focuses on deciphering the genetic and epigenetic mechanisms of gene regulation during development, differentiation and in cancer. His group participates in several EU consortia focusing on epigenetic profiling.

He is the coordinator of BLUEPRINT, an unique European 7th Framework Programme High Impact Project starting October 1st, 2011. BLUEPRINT involve an interdisciplinary network of 42 leading European universities, research institutes and industry entrepreneurs. The BLUEPRINT project is the European cornerstone of the worldwide International Human Epigenome Consortium (IHEC). IHEC seeks to coordinate the production of reference maps of human epigenomes for key cellular states relevant to health and diseases. (http://www.ihec-epigenomes.org/).

7.00 – 8.00 pm

Evening Lecture

Future Medicine: The promise and challenge of translating science into health care

Klaus Lindpaintner

Prof. **Klaus Lindpaintner**, MD, MPH, FACP is Vice President of Research and Development and Chief Scientific Officer at SDIX, a specialty immunosolutions provider active in biomarker science and biotherapeutics.
Previously, he held senior management positions at F Hoffman-La Roche, most recently as Director of the Roche Molecular Medicine Laboratories in Basel, coordinating the company's efforts and activities in implementing biomarker research based on genetics, genomics, proteomics and associated disciplines across the value chain from early discovery to late-stage clinical trials. Professor Lindpaintner has co-authored more than 250 scientific papers, and currently holds honorary and adjunct professorships at several academic institutions. He has served on numerous working groups and advisory panels for trade organizations, regulatory authorities and nongovernmental organizations on issues related to the ethical and societal impact of novel technologies in biomedicine. Professor Lindpaintner graduated from Innsbruck University Medical School with a degree in medicine and from Harvard University with a degree in public health. He pursued post-graduate training and specialization in internal medicine, cardiology, and genetics in the US and Germany and holds board certification in these specialties. He pursued clinical practice in these areas and academic

research in molecular genetics and genetic epidemiology while an Associate Professor of Medicine at Harvard Medical School. He is married to Lyn, an internist-geriatrician, and has two daughters who are pursuing undergraduate and graduate training. In his leisure time he likes to pursue high-altitude mountaineering, photography, and travel.

8.00 – 10.00 pm ***Get-together (Wine, Cheese, Music)***

Wednesday, September 28th, 2011

Symposium IV: Genomics of Infection, Inflammation & Environmental Interaction

9.00 – 9.45 am ***Keynote Presentation***

Impact of the immune system on metastatic breast cancer and chemotherapy efficacy

Karin de Visser

Dr. **Karin E. de Visser** obtained her Ph.D. at the Department of Immunology at the Netherlands Cancer Institute in Amsterdam, where she studied the impact of T cell tolerance on tumor-immunotherapy, under supervision of Dr. Ada Kruisbeek. From 2003-2005 she worked as a post-doctoral fellow of the Dutch Cancer Society in the lab of Dr. Lisa Coussens in the Cancer Research Institute at the University of California, San Francisco, where she developed an active interest in the interplay between adaptive and innate immune system during cancer development. She identified a novel promoting role for B lymphocytes during inflammation-associated skin carcinogenesis. In 2005 she joined the laboratory of Dr. Jos Jonkers at the Division of Molecular Biology at the Netherlands Cancer Institute, where she expanded her research direction into the field of inflammation and mammary carcinogenesis, using conditional mouse models. Currently she has established her own research group at the Division of Molecular Biology at the Netherlands Cancer Institute. Her group studies the role of the innate and adaptive immune system in breast cancer development, metastasis formation and therapy response.

9.45 – 10.00 am ***Impaired host-microbiome crosstalk in inflammatory bowel disease***

Robert Häsler

1995-1996 Study of Biology at the Eberhard Karls University of Tübingen, Germany

1996-1997 Study of Biology at the University of Konstanz, Germany, diploma-thesis (Dipl. Biol) at the Institute of Physiological Chemistry (supervisor Prof. Dr. Dirk Pette)

1997-2001 Ph D. thesis (Dr. rer. nat) in host-pathogen interactions on human skin (supervisor Prof. Dr. Jens Michael Schröder) at the Dept. of Dermatology, University of Kiel, Germany

2001-today PostDoc at the Institute of Clinical Molecular Biology, Christian Albrechts University of Kiel, Germany (head: Prof. Dr. Stefan Schreiber)

2003-today Scientific leader of the platform for functional genomics and expression analysis in the same institute.

Major research projects/fields of interest:

Functional genomics of inflammatory bowel diseases and healthy ageing; epigenetics and epigenomics of chronic inflammation; host microbiome interactions in complex human diseases

10.00 – 10.15 am ***Integrative data analysis of cancer tissues using next generation sequencing***

Martin Kerick

Martin Kerick earned his diploma in experimental Neurobiochemistry (Christian Kaltschmidt) at the University of Witten-Herdecke and his PhD (Hans Lehrach, Stefan Schreiber) at the Max Planck Institute for Molecular Genetics (MPIMG) and the Institute for Clinical and Molecular Biology in Kiel. The focus of his work was gene expression studies in inflammatory bowel diseases. Besides his experimental work he developed a profound interest in the computational analysis of biological data and established diverse tools for the management of high throughput data sets. After two years as a statistician at Eligo GmbH (Berlin), he joined the group of Michal-Ruth Schweiger at the MPIMG (department Vertebrate Genomics) as a postdoctoral fellow. His current interests center on the development of new bioinformatic analysis strategies and the integration of high throughput datasets with a focus on next generation sequencing technologies in cancer research.

10.15 – 10.30 am ***Early detection of colorectal cancer from patient blood plasma using microRNA-based RT-qPCR***

Adam Baker

Dr. **Adam Baker** is the Vice President of Diagnostics and Pharmaceutical Alliances at Exiqon where he leads the diagnostics and companion diagnostic programs.

Exiqon utilize its know-how and technology to address the unmet need for new biomarker based approaches to the diagnosis of many human diseases. The current focus for Adam and his group is to develop sensitive and robust methods for detection of disease related microRNA biomarkers from common clinical source material such as FFPE, plasma and other body fluids.

Adam holds a Ph.D. in Molecular Biology and Genetics from The Research Institute of Molecular Pathology (in Vienna). Following that he did postdoctoral research at Boehringer Ingelheim followed by a senior scientist position at Chromos Molecular Systems Inc. (Vancouver, Canada). Before joining Exiqon Adam headed the department for new technologies at DeCODE Genetics (Iceland) for seven years.

10.30 – 10.45 am **_IG Cellular Systems Genomics: Network analysis of tumor drug resistance_**

Stefan Wiemann

Stefan Wiemann graduated in molecular biology at the biological faculty University of Kaiserslautern and at the German Cancer Research Center Heidelberg (Volker Kinzel). He was visiting scientist at the European Molecular Biology Laboratory (Wilhelm Ansorge) from 1992-1995, where he was involved in the genome sequencing of the first eukaryote (Saccharomyces cerevisiae). He then joined the division Molecular Genome Analysis (Annemarie Poustka) at the DKFZ to set up a systematic cDNA analysis pipeline. Since 2008 he has been head of the division Molecular Genome Analysis and as of 2010 also of the Genomics and Proteomics Core Facility of the DKFZ. He is member of the Project Committee and spokesperson of the NGFN.
He has led research networks in DHGP and NGFN. There, he coordinated the German cDNA Consortium, which was the largest cDNA generation and sequencing initiative in Europe. Building on these cDNA resources, functional genomic projects were established aimed to analyze the localization and activities of encoded proteins. In the recent years, the work in the NGFN has focused on breast cancer development and progression, and on the mechanistic impact proteins and miRNAs have in these processes, putting a particular emphasis on cellular signaling pathways and networks.

10.45 – 12.45 pm **_Lunch Break and Poster Session II_**
(10.45 - 11.45 am odd numbers, 11.45 - 12.45 pm even numbers)

10.45 – 12.45 pm **Company Satellite Sessions:**

11.00 – 11.30 am **Stephen E. Lincoln**, **Complete Genomics**, Inc. Mountain View, California USA
Genome-Wide Detection and Analysis of Germline and Somatic Variations in Tumors

11:35 – 12:05 pm **Goran Tomicic**, **Life Technologies** Corporation
Ion Torrent PGM™ for Clinical Genetics

12.10 – 12.40 pm **Neil Ward**, Sequencing Specialist – EMEA, **Illumina**
Illumina Sequencing - Whole genomes to amplicons

12.45 – 1.00 pm **Poster Award Ceremony:**

12.45 – 1.00 pm **Ceremony: “Annemarie Poustka Poster Award of Medical Genome Research 2011” sponsored by Roche Diagnostics GmbH**

Christine Kuch, Roche Diagnostics Deutschland GmbH
Stefan Wiemann, Speaker Project Committee
of NGFN-Plus / NGFN-Transfer

Symposium VI: Genomics of Cancer

1.00 – 1.15 pm

Human Induced Pluripotent Stem Cells Harbor Homoplasmic and Heteroplasmic Mitochondrial DNA Mutations While Maintaining Human Embryonic Stem Cell-like Metabolic Reprogramming

Alessandro Prigione

Alessandro Prigione, MD PhD, is currently a post-doctoral scientist at the MPI for Molecular Genetics in Berlin, Germany. He received his M.D. at the University of Milan, Italy, in 2002 and subsequently graduated from the International PhD Program in Molecular Medicine at the Vita-Salute San Raffaele University in Milan, Italy, in 2008. Before joining the MPI, Dr. Prigione studied Parkinson's disease at the University of Milan-Bicocca (Italy), mitochondrial disorders at the University of California at Davis (USA), and stem cell biology and cellular reprogramming at the San Raffaele Scientific Institute (Italy). He was recently awarded a Fritz Thyssen grant to develop novel *in vitro* models for diseases affecting the mitochondrial genome by employing human induced pluripotent stem (iPS) cells. His research focuses on the interrelation of mitochondrial biology and "stemness", as well as mitochondrial and metabolic modifications occurring in human embryonic stem cells and upon cellular reprogramming.

1.15 – 1.30 pm

Development of molecular inhibitors targeting hot spots of AML1/ETO dimer-tetramer transition

Christian Wichmann

From 1997-2005 **Christian Wichmann** studied medicine at the Johann Wolfgang Goethe-University of Frankfurt am Main. 2000-2002 he performed his thesis at the department of Hematology, University of Frankfurt supervised by Prof. Dr. Dieter Hoelzer with the title: „Influence of the translocation product STAT5/RARα on proliferation and differentiation of hematopoietic cells". Thereafter he joined the laboratory of Prof. Dr. James N. Ihle, St. Jude Children's Research Hospital, Department of Biochemistry in Memphis/USA as a research scholar and studied the role of the centrosomal protein TACC2 in the mouse development. Since 2006 he works as a research associate at the Georg-Speyer-Haus, Frankfurt am Main, in the group of Dr. Manuel Grez. In the lab of Dr. Grez he focuses on the analysis of AML1/ETO complex composition and selective interference with its leukemogenic function. His further scientific interests are mechanisms of normal and leukemic CD34+ progenitor cell expansion.

1.30 – 1.45 pm ***miRNAs in prostate cancer***

Ruprecht Kuner

Ruprecht Kuner studied biology at the Eberhard Karls University in Tübingen (1991-1998) focused on human genetics and virology. He received his Ph.D. in molecular biology at the Humboldt University Berlin (2002) by searching for tumor-associated genes in gynecological cancer. From 2003-2010, he worked as a scientist in the Division of Molecular Genome Analysis at the DKFZ in Heidelberg. One major topic was the identification of denominator genes involved in human diseases like cardiomyopathies and cancer. Since 2010, he works as senior scientist in the DKFZ group Cancer Genome Research at the National Center of Cancer Diseases (NCT). The present translational research projects comprise diverse Omics technologies and cellular models for the investigation of molecular targets in prostate and lung cancer. A major goal is the identification of robust diagnostic and prognostic genes, miRNAs and signatures in tumor tissues and patients' surrogates.

1.45 – 2.15 am ***Coffee Break***

2.15 – 2.30 pm ***Affinity-based proteomic analysis of pancreatic cancer***

Jörg Hoheisel

Jörg D. Hoheisel is Head of the *Division of Functional Genome Analysis* at the Deutsches Krebsforschungszentrum (DKFZ; German Cancer Research Center) in Heidelberg. He also holds the position of chairman of the Scientific Council of DKFZ. His division is active in establishing and applying analyses at the levels of DNA, RNA and proteins toward early and personalised diagnosis and prognosis of cancer, identification of new therapy approaches and monitoring of treatment success, with a focus on pancreatic cancer.

Prior to joining DKFZ in 1993, Jörg worked for five years 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 on the subjects of analysing different, topologically induced DNA-structures and the functioning of DNA-binding enzymes.

(www.dkfz.de/funct_genome/)

2.30 – 2.45 pm

Multiple (epi)genetic modifier loci of Apcmin-induced tumourigenesis identified using chromosome substitution strains

Alexandra Farrall

In 2009 **Alexandra Farrall** completed her PhD in the Dept. Biochemistry, at the University of Adelaide, Australia, with Prof. Murray Whitelaw, and in collaboration with Prof. Lorenz Poellinger, Karolinksa Insitute, Stockholm, investigating novel transcriptional regulatory roles of the bHLH-PAS transcription family member, SIM2, including roles in prostate and pancreatic tumourigenesis. Subsequently she commenced a post-doctoral research fellowship at the Max Planck Institute for Molecular Genetics, Berlin, with Prof. Bernhard Herrmann and Dr. Markus Morkel investigating (epi)genetic modifier´s of tumour development and (cancer) stem cell function in ApcMin-induced intestinal cancer in the mouse.

2.45 – 3.30 pm

Keynote Presentation

Cancer Genome Analysis in Chronic Lymphocytic Leukemia

Ivo Gut

Ivo Gut qualified in Chemistry at the University of Basel and obtained a PhD in Physical Chemistry from the same University with Prof. Jakob Wirz in 1990. From 1990 on he was as research fellow in the group of Prof. Irene Kochevar at Harvard Medical School.
Between 1993 and 1996 he was research fellow with Dr. Stephan Beck at the Imperial Cancer Research Fund in London. Later, at the Max-Planck-Institute for Molecular Genetics he led a group in the Department for Vertebrate Genomics of Prof. Hans Lehrach. The 11 years before joining the CNAG he was at the Centre National de Génotypage (CEA) first as Head of Technology Development and later as Associate Director under Prof. Mark Lathrop.
His research interests are genomics, genetics, high-throughput nucleic acid analysis methods, proteomics, implementation of -omics methods, automation and data analysis.
Ivo Gut is author of more than 125 research papers, inventor of 24 patents or patent applications and founder of 4 biotech companies (Genom Analytik GmbH, Biopsytec GmbH and Epigenomics AG, Integragen SA).
He is the coordinator of the 12M€ EU FP7-funded Integrated Project READNA on DNA sequencing technology.

3.30 – 3.45 pm

Concluding Remarks: Markus Nöthen, Friedrich-Wilhelms University, Bonn, Speaker Project Committee of NGFN-Plus / NGFN-Transfer in the Program of Medical Genome Research

Overviews

Oral Presentations

Page	Abstract	Presenting Author	Abstract Title	Consortium
		Symposium I - Genomics of Genomics of CNS Disorders		
82	I-Keynote	Julie Williams	Defining the genetic Architecture of Alzheimer's Disease	
83	O-I-1	Günter Höglinger	Identification of common variants influencing risk of the tauopathy Progressive Supranuclear Palsy	IG Functional Genomics of Parkinson
84	O-I-2	Aaron Voigt	The Mitochondrial Chaperone Protein TRAP1 Mitigates α-Synuclein Toxicity	IG Functional Genomics of Parkinson
85	O-I-3	Sandra Meier	Association between negative mood delusions in bipolar disorder and genetic variations in 3q26.1	IG Molecular Causes of Major Mood Disorders and Schizophrenia (MooDS)
86	O-I-4	Hans-Hilger Ropers	Deep sequencing reveals 50 novel genes for recessive cognitive disorders	IG German Mental Retardation Network (MRNET)
87	O-I-5	Elisabeth Graf	Exome Sequencing Reveals a Mutation in the Retromer Protein VPS35 as Cause for Late-Onset Parkinson"s Disease	IG German Mental Retardation Network (MRNET)
		Symposium II - Genomics of Cardiac Disease and Metabolism		
90	II-Keynote	Leif Groop	Genetics of type 2 diabetes- quo vadis?	
91	O-II-1	Christian Gieger	Human metabolic individuality in biomedical and pharmaceutical research	NGFN-2 / -1
92	O-II-2	Nadja Knoll	Gene set of nuclear encoded mitochondrial regulators is enriched for inherited variation in obesity	IG Molecular Mechanisms in Obesity
93	O-II-3	Benjamin Meder	Genome-wide association study identifies novel risk locus for dilated cardiomyopathy	IA Subgenome Fractionation for High Throughput Sequencing
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100	O-III-2	Angelika Daser	High throughput copy number counting in single cells – a method for the detection of meiotic and mitotic errors	
101	O-III-3	Hans Lehrach	The IT Future of Medicine – a flagship initiative to revolutionize our health care system	IG Systems Biology of Genetic Diseases (Mutanom)
102	O-III-4	Martin Hrabé de Angelis	Next steps in systemic analysis of mouse mutants at the German Mouse Clinic	IG German Mouse Clinic - Deciphering Comorbidity in Human Disease Models
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111	O-IV-3	Adam Baker	Early detection of colorectal cancer from patient blood plasma using microRNA-based RT-qPCR	Exiqon A/S
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119	O-V-4	Jörg D. Hoheisel	Affinity-based proteomic analysis of pancreatic cancer	IG Genome Research Network in Pancreatic Cancer
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138	P-I-13	Daniela Vogt Weisenhorn	Gain and Loss of Lrrk2 - Two Mouse Models of Parkinson´s Disease	IG Functional Genomics of Parkinson
139	P-I-14	M. Höllerhage	Wild-type alpha-synuclein leads to cell death in postmitotic human dopaminergic neurons.	IG Functional Genomics of Parkinson
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Oral Presentation Abstracts

Oral Presentation Abstracts

Symposium I

Genomics of CNS Disorders

Defining the Genetic Architecture of Alzheimer's Disease

Presenting Author: Julie Williams

Cardiff University School of Medicine, Cardiff, UK

820,000 individuals in the UK have dementia and this number is estimated to double in the next generation. Alzheimer's disease (AD) is the most common form of dementia which is caused by a combination of genetic and environmental factors. AD is genetically complex but does show evidence of strong heritability. Variants of three genes (APP, PS-1 & 2) are known to contribute to rare, predominantly early onset forms of AD. Until recently, variation at the APOE locus was the only common risk factor for AD. In 2009 we published evidence for two new susceptibility genes (Harold et al, Nat. Genet.) CLU and PICALM using a powerful genome-wide association approach. When we put our data together with a GWAS from a French group (Lambert et al, 2009; Nat. Genet.) a third gene CR1 was confirmed. In addition our collaborative group GERAD (GERAD: Genetic and Environmental Risk in Alzheimer's disease) have identified compelling evidence for a further 5 susceptibility genes for Alzheimer's disease (Hollingworth et al, 2011, Nat. Genet.). These genes highlight several potential disease mechanisms, including endocytosis, immune response and lipid processing. This presentation will describe these findings and highlight important areas for future research.

Identification of common variants influencing risk of the tauopathy Progressive Supranuclear Palsy

Presenting Author: Günter Höglinger
Günter U. Höglinger (1), Nadine M. Melhem (2), Dennis W. Dickson (3), Patrick M.A. Sleiman (4), Li-San Wang (5), Lambertus Klei (2), Rosa Rademakers (3), Rohan de Silva (6), Irene Litvan (7), David E. Riley (8), John C. van Swieten (9), Peter Heutink (10), Zbigniew K. Wszolek (11), Ryan J. Uitti (11), Jana Vandrovcova (6), Howard I. Hurtig (12), Rachel G. Gross (12), Walter Maetzler (13,14), Stefano Goldwurm (15), Eduardo Tolosa (16), Barbara Borroni (17), Pau Pastor (18,19,20), PSP Genetics Study Group, Laura B. Cantwell (5), Mi Ryung Han (5), Allissa Dillman (21), Marcel P. van der Brug (22), J Raphael Gibbs (6,21), Mark R. Cookson (21), Dena G. Hernandez (6,21), Andrew B. Singleton (21), Matthew J. Farrer (23), Chang-En Yu (24,25), Lawrence I. Golbe (26), Tamas Revesz (27), John Hardy (6), Andrew J. Lees (6,27), Bernie Devlin (2), Hakon Hakonarson (4), Ulrich Müller (28), Gerard D. Schellenberg (5)

(1) Dept. of Neurology, Philipps-Universität, Marburg, (2) Dept. of Psychiatry, Univ. of Pittsburgh, Pennsylvania, USA, (3) Dept. of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA, (4) Center for Applied Genomics, Childrens Hospital, Philadelphia, Pennsylvania, USA, (5) Dept. of Pathology and Laboratory Medicine, Univ. of Pennsylvania, Philadelphia, USA, (6) Reta Lila Weston Inst., UCL Institute of Neurology, London, UK, (7) Dept. of Neurology, Univ. of Louisville, Kentucky, USA, (8) Dept. of Neurology, Case Western Reserve Univ., Cleveland, Ohio, USA, (9) Dept. of Neurology, Erasmus Univ., Rotterdam, Netherlands, (10) Dept. of Clinical Genetics, VU Univ., Amsterdam, Netherlands, (11) Dept. of Neurology, Mayo Clinic, Jacksonville, Florida, USA, (12) Dept. of Neurology, Univ. of Pennsylvania, Philadelphia, Pennsylvania, USA, (13) Dept. of Neurology, Hertie Institute, Univ. of Tübingen, Germany, (14) DZNE, Tübingen, Germany, (15) Parkinson Institute, Istituti Clinici di Perfezionamento, Milano, Italy, (16) Neurology Service, Universitat de Barcelona, Spain, (17) Dept. of Neurology, Univ. of Brescia, Italy, (18) CIBERNED, Instituto de Salud Carlos III, Madrid, Spain, (19) Neurogenetics laboratory, Univ. of Navarra, Pamplona, Spain, (20) Dept. of Neurology, Univ. of Navarra, Pamplona, Spain, (21) Laboratory of Neurogenetics, National Institutes of Health, Bethesda, Maryland, USA, (22) Department of Neuroscience, The Scripps Research Institute, Jupiter, Florida, USA, (23) Department of Medical Genetics, Univ. of British Columbia, Vancouver, Canada, (24) Department of Medicine, Univ. of Washington, Seattle, Washington, USA, (25) Veterans Affairs Puget Sound Health Care System, Seattle, Washington, USA, (26) Dept. of Neurology, Johnson Medical School, New Brunswick, New Jersey, USA, (27) Queen Square Brain Bank for Neurological Disorders, UCL, London, UK, (28) Institut for Humangenetik, Justus-Liebig-Universität, Giessen, Germany.

Progressive supranuclear palsy (PSP) is a movement disorder with prominent tau neuropathology. Brain diseases with abnormal tau deposits are called tauopathies, the most common being Alzheimer's disease. Environmental causes of tauopathies include repetitive head trauma associated with some sports. To identify common genetic variation contributing to risk for tauopathies, we carried out a genome-wide association study of 1,114 PSP cases and 3,247 controls (Stage 1) followed up by a second stage where 1,051 cases and 3,560 controls were genotyped for Stage 1 SNPs that yielded $P = 10^{-3}$. We found significant novel signals ($P < 5 \times 10^{-8}$) associated with PSP risk at STX6, EIF2AK3, and MOBP. We confirmed two independent variants in MAPT affecting risk for PSP, one of which influences MAPT brain expression. The genes implicated encode proteins for vesicle-membrane fusion at the Golgi-endosomal interface, for the endoplasmic reticulum unfolded protein response, and for a myelin structural component.

The Mitochondrial Chaperone Protein TRAP1 Mitigates α-Synuclein Toxicity

Presenting Author: Aaron Voigt
Aaron Voigt (1), Erin K. Butler (1), Kathrin A Lutz (2), Peter Karsten (1) Konstanze, Winklhofer (2), Jörg B. Schulz (1)

(1) University Medical Center, RWTH Aachen, Department of Neurology

(2) Adolf Butenandt Institute, Ludwig Maximilians University, Department of Neurobiochemistry

Mutations in the pre-synaptic protein, α-Synuclein (SNCA, PARK1/4), result in autosomal dominant, inherited Parkinson's Disease (PD). Overexpression or mutation of α-Synuclein is associated with protein aggregation and interferes with a number of cellular processes, including mitochondrial integrity and function. We used a whole-genome screen in Drosophila to search for novel genetic modifiers of human [A53T]α-Synuclein-induced neurotoxicity. Decreased expression of the mitochondrial chaperone TRAP1 was found to enhance aging-dependent loss of brain dopamine (DA) and DA neuron number resulting from [A53T]α-Synuclein expression. In addition, decreased TRAP1 levels in [A53T]α-Synuclein-expressing flies resulted in enhanced loss of climbing ability and sensitivity to oxidative stress. Overexpression of human TRAP1 was able to rescue these phenotypes. Similarly, overexpression of human TRAP1 and in rat primary cortical neurons rescued [A53T]α-Synuclein induced sensitivity to rotenone treatment. In human embryonic kidney (HEK293) cells, silencing of TRAP1 enhanced [A53T]α-Synuclein-induced sensitivity to oxidative stress treatment. [A53T]α-Synuclein directly interfered with mitochondrial function, as its expression reduced Complex I activity in HEK293 cells. These effects were blocked by TRAP1 overexpression. Moreover, TRAP1 was able to prevent alteration in mitochondrial morphology caused by [A53T]α-Synuclein overexpression in human SH-SY5Y cells. These results indicate that [A53T]α-Synuclein toxicity is intimately connected to that of mitochondrial dysfunction and that toxicity reduction in fly, rat primary neurons and human cell lines can be achieved using overexpression of TRAP1. Interestingly, TRAP1 has previously been shown to be phosphorylated by the serine/threonine kinase PINK1, thus linking PINK1 via TRAP1 to α-Synuclein, providing mechanistic insights into the pathology of PD.

Association between negative mood delusions in bipolar disorder and genetic variations in 3q26.1

Presenting Author: Sandra Meier
Sandra Meier(1), Manuel Mattheisen(2,3,4), Evangelos Vassos(5), Jana Strohmaier(1), Jens Treutlein(1), Frank Josef(1), René Breuer(1), Franziska A. Degenhardt(2,3), Thomas W. Mühleisen(2,3), Bertram Müller-Myhsok(6), Michael Steffens(4), Christine Schmael(1), Markus M. Nöthen(2,3), Sven Cichon(2,7), Thomas G. Schulze(8), Marcella Rietschel(1)

(1)Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, University of Heidelberg, J5, 68159 Mannheim, Germany

(2)Department of Genomics, Life & Brain Center, University of Bonn, Sigmund-Freud-Str. 25, 53127 Bonn, Germany

(3)Institute of Human Genetics, University of Bonn, Sigmund-Freud-Str. 25, 53127 Bonn, Germany

(4)Institute for Medical Biometry, Informatics, and Epidemiology, University of Bonn, Sigmund-Freud-Str. 25, 53127 Bonn, Germany

(5)Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King"s College London, London, United Kingdom

(6)Max-Planck-Institute of Psychiatry,Department of Statistical Genetics, Kraepelinstr.2, 80804 Munich, Germany

(7)Department of Psychiatry and Psychotherapy, University Medical Center, Georg-August-University, Von-Siebold-Str. 5, 37075 Göttingen, Germany

(8)Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Leo-Brandt-Strasse 5, 52425 Juelich, Germany

Previous research has suggested that clinical symptom dimensions may be useful for delineating the genetics of bipolar disorder (BD) than standard diagnostic models. This concept has not yet been applied to data from genome-wide association studies (GWAS) of BD. The aim of the present study was to perform a GWAS of factor dimensions in 637 clinically well-characterized BD patients of German ancestry. In a subsequent follow-up study of our top dimensional GWAS results, an additional 290 German BD patients were included. Rs9875793, which is located in an intergenic region of 3q26.1 in vicinity to solute carrier family 2 (facilitated glucose transporter), member 2 gene (SLC2A2), was significantly associated with the factor dimension “Negative Mood Delusions” in the combined BD sample (n= 927; P= 4.65 x 10^{-8}, OR= 2.66). Testing this variant in 104 bipolar patients, who displayed symptoms loading on “Negative Mood Delusions” factor dimension, revealed an overrepresentation of the rs9875793 G allele (P= 0.0007, OR= 1.74) compared to controls. Currently we aim to replicate this association finding in independent samples.

Deep sequencing reveals 50 novel genes for recessive cognitive disorders

Presenting Author: Hans-Hilger Ropers
Hossein Najmabadi (1), Hao Hu (2,*), Masoud Garshasbi (1,2,*), Tomasz Zemojtel (3), Seyedeh Sedigheh Abedini (1), Wei Chen (2,4), Masoumeh Hosseini (1), Farkhondeh Behjati (1), Stefan Haas (3), Payman Jamali (5), Agnes Zecha (2), Marzieh Mohseni (1), Lucia Püttmann (2), Leyla Nouri Vahid (1), Corinna Jensen (2), Lia Abbasi Moheb (1,2), Melanie Bienek (2), Farzaneh Larti (1), Ines Mueller (2), Robert Weissmann (2), Hossein Darvish (1), Klaus Wrogemann (2,14), Valeh Hadavi (6), Bettina Lipkowitz (2), Sahar Esmaeeli-Nieh (2), Dagmar Wieczorek (7), Roxana Kariminejad (6), Saghar Ghasemi Firouzabadi (1), Monika Cohen (8), Zohreh Fattahi (1), Imma Rost (9), Faezeh Mojahedi (10), Christoph Hertzberg (11), Atefeh Dehghan (12), Anna Rajab (13), Mohammad Javad Soltani Banavandi (1), Julia Hoffer (2), Masoumeh Falah (1), Luciana Musante (2), Vera Kalscheuer (2), Reinhard Ullmann (2), Andreas Walter Kuss (2), Andreas Tzschach (2), Kimia Kahrizi (1) H. Hilger Ropers (2)

(1) Genetics Research Center, University for Social Welfare and Rehabilitation Sciences, Tehran, Iran, (2) Department Human Molecular Genetics, Max Planck Institute for Molecular Genetics, 14195 Berlin, Germany, (3) Department of Computational Molecular Biology, Max Planck Institute for Molecular Genetics, 14195 Berlin, Germany, (4) Max-Delbrueck-Centrum fuer Molekulare Medizin, 13092 Berlin, Germany, (5) Shahroud Welfare Organization, Semnan, Tehran, Iran, (6) Kariminejad-Najmabadi Pathology and Genetics Centre, Tehran, Iran, (7) Institut fuer Humangenetik, Universitaetsklinikum, 45122 Essen, Germany, (8) Kinderzentrum Muenchen, 81377 Muenchen, Germany, (9) Zentrum fuer Humangenetik und Laboratoriumsmedizin Dr. Klein und Dr Rost, 82152 Martinsried, Germany, (10) Mashad Welfare Organization, Mashad, Iran, (11) Kinderneurologie und Sozialpaediatrie, Vivantes-Klinikum Neukölln, 12351 Berlin, Germany, (12) Yazd Welfare Organization, Yazd, Iran, (13) Genetics Unit, Ministry of Health, Directorate General of Health Affairs, Royal Hospital, Muscat, Oman, (14) Department of Biochemistry & Medical Genetics, University of Manitoba, Winnipeg, MB Canada,

*** equal contribution**

Common diseases are often complex because they are genetically heterogeneous, with many different genetic defects giving rise to clinically indistinguishable phenotypes. This has been amply documented for intellectual disability (ID), one of the most complex disorders known and a very important health care problem world-wide. More than 90 different gene defects have been identified for X-linked ID alone, but research into the more frequent autosomal forms of ID is still in its infancy. To expedite the molecular elucidation of autosomal recessive ID, we have now performed homozygosity mapping, exon enrichment and next generation sequencing in 136 consanguineous families with autosomal recessive ID from Iran and elsewhere. This study, by far the largest published to date, has revealed additional mutations in 23 genes implicated previously in ID or related neurological disorders, as well as single, probably disease-causing variants in 50 novel candidate genes. Several of these interact directly with known ID genes, and many are involved in fundamental cellular processes such as transcription and translation, cell cycle control, energy metabolism and fatty acid synthesis, which seem to be pivotal for normal brain development and function.

Exome Sequencing Reveals a Mutation in the Retromer Protein VPS35 as Cause for Late-Onset Parkinson's Disease

Presenting Author: Elisabeth Graf

Elisabeth Graf (1), Alexander Zimprich (2), Anna Benet-Pagès (1), Walter Struhal (3), Sebastian H Eck (1), Marc N Offman (4), Dietrich Haubenberger (2), Sabine Spielberger (5), Eva C Schulte (1,6), Peter Lichtner (1), Shaila C Rossle (4), Norman Klopp (7), Elisabeth Wolf (5), Klaus Seppi (5), Walter Pirker (2), Stefan Presslauer (8), Brit Mollenhauer (9), Regina Katzenschlager (10), Thomas Foki (2), Christoph Hotzy (2), Eva Reinthaler (2), Ashot Harutyunyan (11), Robert Kralovics (11), Annette Peters (7), Fritz Zimprich (2), Thomas Brücke (8), Werner Poewe (5), Eduard Auff (2), Claudia Trenkwalder (9,12), Burkhard Rost (4), Gerhard Ransmayr (3), Juliane Winkelmann (2, 6 , 13), Thomas Meitinger (1,13), Tim M Strom (1,13).

(1) Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany, (2) Department of Neurology, Medizinische Universität Wien, Vienna, Austria, (3) Department of Neurology and Psychiatry, Allgemeines Krankenhaus, Linz, Austria, (4) Institute of Bioinformatics, Technische Universität München, Munich, Germany, (5) Department of Neurology, Medizinische Universität Innsbruck, Innsbruck, Austria, (6) Department of Neurology, Technische Universität München, Munich, Germany, (7) Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany, (8) Department of Neurology, Wilhelminenspital, Vienna, Austria, (9) Paracelsus-Elena Klinik, Kassel, Germany, (10) Department of Neurology, Sozialmedizinisches Zentrum Ost-Donauspital, Vienna, Austria, (11) Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria, (12) Department of Clinical Neurophysiology, Georg-August-Universität Göttingen, Göttingen, Germany, (13) Institute of Human Genetics, Technische Universität München, Munich, Germany

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by motor and non-motor symptoms due to the loss of dopaminergic neurons. To identify rare causal variants in late-onset PD, we investigated a family from Austria with 16 affected individuals by exome sequencing. We identified a missense mutation, D620N, in the retromer protein VPS35 which co-segregates with the disease in all seven affected family members that are alive. Genotyping of the identified variant in additional PD cases revealed two further families carrying the mutation. Haplotype analysis shows a common region of 65kb across VPS35 in the three families. Screening of all coding exons of VPS35 in additional cases and controls revealed six further non-synonymous variants. Three were unique to PD cases, two were only present in controls, and one present in cases and controls. Because the crystal structure of VPS35 has been partially resolved, we could perform molecular dynamics simulation revealing a large impact on protein stability for two mutations, D620N and R524W. In addition, sequence-based analysis predicted these mutations to be damaging. VPS35 is a subunit of the retromer complex which consists of the cargo-recognition VPS26-VPS29-VPS35 heterotrimer and a membrane-targeting heterodimer or homodimer of SNX1 and/or SNX2. It mediates retrograde transport between endosomes and the trans-Golgi network. Most interesting in our context is the retromer mediated transport of SORL1 that has been implicated in Alzheimer's disease. We are currently performing co-localization studies in HeLa and COS-7 cells to test whether R524W, D620N and L774M variants affect VPS35 protein interactions with VPS26, VPS29, SNX1 and it's cellular localization. A cooperating group is establishing a Drosophila melanogaster model for the variants to investigate the mutational impact on neurodegeneration. VPS35 is, after LRRK2 and SCNA, the third gene in which mutations provide a high risk for late-onset PD.

Oral Presentation Abstracts

Symposium II

Genomics of Cardiac Disease and Metabolism

Genetics of type 2 diabetes - quo vadis?

Presenting Author: Leif Groop

Lund University Diabetes Centre, Malmö, Sweden

During the last 30 years the world has faced a formidable epidemic of obesity and type 2 diabetes. It is clear that the genes have not changed during this short period of time. The logical conclusion would then be that it is all due to the change in the environment. But genes determine how we respond to the environment and genes change in response to the environment as seen for the lactase gene. This gene started to mutate with the domestication of cattle to allow adults to be able to utilize energy from cow milk.
The picture of the genetics of type 2 diabetes (T2D) has dramatically changed with the introduction of whole genome wide association studies (GWAS). Today we know about 40 gene variants which are consistently associated with T2D. This list includes among others TCF7L2 (the No 1 T2D gene), PPARG, KCJN11, CDKAL1, IGFBP2, CDKN2A/CDKN2B,HHEX, SCL30A8, FTO, WSF1, MTNR1B etc. Also studies on glucose-related traits have shown that variants in G6PC, GCK, GCKR and GIPR are associated with glucose and insulin levels. Common to most of these variants is that they seem to result in impaired beta-cell function. Individuals who carry these variants seem to be unable to increase their insulin secretion in response to an increase in BMI and insulin resistance to maintain glucose tolerance normal. A central question has been whether these variants can be used to predict incident T2D. It is premature to start to use these genetic variants for prediction of T2D as we have only been able to explain a small proportion of the familial risk of T2D and even risk scores based upon 40 different variants only marginally increase the predictive value of clinical risk factors like family history of diabetes, BMI and glucose. However, the genetic risk markers perform better the earlier they are used (Lyssenko V. et al. NEJM 392;220, 2008) and pave the way for real primary prevention. We shall though not underestimate the importance of dissecting novel biological pathways for the pathogenesis of T2D, some of which might become potential new drug targets. An important step will also be to use the genetic information for prediction of disease progression, development of complications and response to treatment, i.e. a step towards individualized medicine.

Human metabolic individuality in biomedical and pharmaceutical research

Presenting Author: Christian Gieger
Christian Gieger (1), So-Youn Shin (2), Ann-Kristin Petersen (1), Guangju Zhai (3), Tim D Spector (3), Nicole Soranzo (2), Karsten Suhre (4,5,6)

(1) Institute of Genetic Epidemiology, Helmholtz Zentrum Munich, German Research Center for Environmental Health, Neuherberg, German, (2) The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton UK, (3) Department of Twin Research & Genetic Epidemiology, King's College London, UK, (4) Institute of Bioinformatics and Systems Biology, Helmholtz Zentrum Munich, German Research Center for Environmental Health, Neuherberg, Germany, (5) Faculty of Biology, Ludwig-Maximilians-Universität, Planegg-Martinsried, Germany, (6) Department of Physiology and Biophysics, Weill Cornell Medical College in Qatar, Education City - Qatar Foundation, Doha, Qatar

The better understanding of mechanisms controlling human health and disease, in particular the role of genetic predispositions and their interaction with environmental factors, is a prerequisite for the development of safe and efficient therapies for complex disorders, such as type 2 diabetes and cardiovascular disease. Genome wide association studies (GWAS) have identified many risk loci for complex diseases, but effect sizes are generally small and information on the underlying biological processes is often lacking. Associations with metabolic traits as functional intermediates can overcome many of these problems and potentially inform individualized therapy. Advances in analytical biochemistry have made it possible to obtain global snapshots of metabolism allowing for GWAS with broad panels of metabolite concentrations in different body fluids, like blood serum, plasma or urine. In a series of GWAS we have identified more than 40 genetic loci, typically explaining a large fraction of the variation of the associated metabolic trait. In the majority of cases a protein biochemically related to the associated metabolic traits is encoded at these loci. We present results from our recent study in the German KORA study and the British TwinsUK study (N = 2,800). These associations provide new functional insights for many disease-related associations that have been reported in previous studies, including cardiovascular and kidney disorders, type 2 diabetes, cancer, gout, venous thromboembolism, and Crohn's disease. Our results show the high power and the ability of genetically determined metabotypes to better characterize risk factors. To make this resource available for the scientific community, we have implemented a freely available database to query newly discovered risk loci.

Reference:

Suhre K. et al. Human metabolic individuality in biomedical and pharmaceutical research. Nature in press.

Gene set of nuclear encoded mitochondrial regulators is enriched for inherited variation in obesity

Presenting Author: Nadja Knoll
Nadja Knoll (1), Ivonne Jarick (2), André Scherag (3), Anna-Lena Volckmar (1), Martin Klingenspor (4), Thomas Illig (5), Harald Grallert (5), Christian Gieger (5), H.-Erich Wichmann (6,7,8), Annette Peters (6), Johannes Hebebrand (1), Anke Hinney (1)

(1) Department of Child and Adolescent Psychiatry, University of Duisburg-Essen, Essen, Germany, (2) Institute of Medical Biometry and Epidemiology, Philipps-University of Marburg, Marburg, Germany, (3) Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, Germany, (4) Molecular Nutritional Medicine, Technische Universität München, Else Kröner-Fresenius Center, Freising-Weihenstephan, Germany, (5) Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany, (6) Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany, (7) Institute of Medical Informatics, Biometry, and Epidemiology, Chair of Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany, (8) Klinikum Grosshadern, Munich, Germany

Introduction: Mitochondrial function is altered in obesity. Nuclear encoded human genes are relevant for mitochondrial function [3 gene sets of known relevant pathways: 1) 16 nuclear regulators of mitochondrial genes, 2) 91 genes for oxidative phosphorylation (OXPHOS) and 3) 965 nuclear-encoded mitochondrial genes]. Gene set enrichment analysis (GSEA) showed no association with type 2 diabetes mellitus in these gene sets. We performed a GSEA for the same gene sets for obesity.
Subjects and methods: The GSEA was performed for a genome wide association study (GWAS) on 705 obesity trios (i.e. one extremely obese child or adolescent and both biological parents; Jarick et al., Hum Mol Genet 2011). For confirmation we analyzed an independent case-control (CC) GWAS sample of 453 extremely obese children and adolescents and 435 lean adult controls (Hinney et al., PLoS One 2007), as well as the population-based KORA GWAS sample (n=1743). All three GWAS samples were genotyped with the Affymetrix Genome-Wide Human SNP Array 6.0. In each sample, the distribution of significance levels between the respective gene set and those of all genes was compared with a leading-edge-fraction-comparison test (cutoff = 95th percentile of the set of all gene-wise corrected p-values).
Results: In the 705 trios, nominally significant enrichment of associations for early onset extreme obesity was observed in the set of the 16 nuclear regulators of mitochondrial genes (P = 0.042; p-values = 95th percentile). This finding was confirmed in the KORA sample, whereas in the CC sample only an enrichment of moderate associations (p-values between the 50th and 90th percentiles) was observed.
Conclusion: The GSEA revealed that association signals for obesity were enriched in the gene set of 16 nuclear regulators of mitochondrial genes.

Genome-wide association study identifies novel risk locus for dilated cardiomyopathy

Presenting Author: Benjamin Meder
Benjamin Meder (1)*, Frank Rühle (2)*, Tanja Weis (1)*, Jennifer Franke (1), Andreas Huge (2), Britta Vogel (1), Karen Frese (1), Jan Haas (1), Anika Witten (2), Philipp Ehlermann (1), Christian Zugck (1), Frauke Friedrichs (2), Justo Lorenzo Bermejo (10), Barbara Peil (10), Georg Homuth (12), Uwe Völker (12), Heyo Kroemer (15), Marcus Dörr (9), Wolfgang Hoffmann (14), Bernhard Maisch (11), Sabine Pankuweit (11), Volker Ruppert (11), Thomas Scheffold (16), Uwe Kühl (17), Hans-Peter Schultheiss (17), Reinhold Kreutz (21), Boris Ivandic (1), Dieter Weichenhan (13), Nour-Eddine El-Mokhtari (4), Stefan Schreiber (4), Stephan Felix (9), Gerd Hasenfuß (7), Arne Pfeufer (5), Andreas Keller (20), Norbert Hübner (19), Stefan Kääb (5), Eloisa Arbustini (8), Wolfgang Rottbauer (3), Norbert Frey (6), Monika Stoll (2) and Hugo A. Katus (1)

1 Department of Internal Medicine III, University Hospital Heidelberg, Heidelberg, Germany, 2 Genetic Epidemiology of Vascular Disorders, Leibniz-Institute for Arteriosclerosis Research at the University Münster, Münster, Germany, 3 Department of Internal Medicine II, University of Ulm, Ulm, Germany, 4 Christian-Albrechts-University Kiel, PopGen Biobank, Kiel, Germany, 5 Institute of Human Genetics, Genome Research Center for Enviromental Health, Technical University Munich and Helmholtz Center Munich, Munich, Germany, 6 Department of Internal Medicine, University of Kiel, Kiel, Germany, 7 Department of Cardiology and Pneumology, University of Göttingen, Göttingen, Germany, 8 Molecular Diagnostic Division, IRCCS Policlinico San Matteo, Pavia, Italy, 9 Department of Internal Medicine B, Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany, 10 Institute of Medical Biometry and Informatics (IMBI), University Hospital Heidelberg, Germany, 11 Department of Cardiology, University Hospital of Marburg, Marburg, Germany, 12 Institute of Genetics and Functional Genomic Research, Greifswald, Germany, 13 German Cancer Research Center (DKFZ), Heidelberg, Germany, 14 Institute of Community Medicine, Greifswald, Germany, 15 Institute of Pharmacology, Greifswald, Germany, 16 Institute for Heart and Circulation Research, University Witten/Herdecke, Dortmund, Germany, 17 Department of Cardiology and Pneumonology, Charité Centrum 11 for Cardiovascular Medicine, Charité, Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany, 18 Institut of Clinical Pharmacology and Toxicology, Charitéplatz 1, 10117 Berlin, Germany, 19 Max Delbrück Center for Molecular Medicine, Berlin-Buch, Germany, 20 Department of Human Genetics, Saarland University, Germany, 21Department for Pharmacology, Charité, Universitätsmedizin Berlin, Berlin, Germany

Dilated Cardiomyopathy (DCM) is one of the most prevalent heart diseases and belongs to the most common causes of cardiac death in western civilizations. It is estimated that 20-35% of DCM cases are caused genetically, but despite much effort, the genetic contribution remains unclear in many cases. Here we present results from a three-staged genome wide association study (GWAS) including more than 3,000 DCM cases and 7,000 controls in total. The study comprises a genome wide screening stage of 910 cases (2120 controls) and two independent replication stages of 2237 (4081) and 483 (785) cases (controls), respectively. We identified DCM-associated SNPs on chromosome 6 and 12 with genome-wide significance in the screening stage. Among these we have found multiple associated SNPs on chromosome 6 in close linkage disequilibrium, which could be successfully replicated. The strongest associated SNP shows an odds ratio (OR) of 1.48 (95% CI 1.30 – 1.69) for carriers of the minor allele. Within or close to the associated locus we find several inflammatory genes, suggesting a genetically driven, partially inflammatory pathogenesis of DCM.

Investigation of the coronary artery disease risk gene ADAMTS-7 in a murine knockout-model

Presenting Author: Thorsten Kessler
Zouhair Aherrahrou (1,*), Thorsten Kessler (1, *), Kjestine Schmidt (2), Cor de Wit (2), Heribert Schunkert (1) & Jeanette Erdmann (1)

(1) Universität zu Lübeck, Medizinische Klinik II, , Ratzeburger Allee 160, 23562 Lübeck, Germany

(2) Universität zu Lübeck, Institut für Physiologie, , Ratzeburger Allee 160, 23562 Lübeck, Germany

(*) These authors contributed equally to this work

INTRODUCTION: Recently, our group identified association of several genes with coronary artery disease (CAD) by genome wide association studies (GWAS). One of these risk genes is encoding the proteinase ADAMTS-7 which thus far has mainly been investigated in the context of arthritis but not CAD. Interestingly, the risk allele is rather associated with formation of artery stenosis than myocardial infarction (MI). Until now, the pathomechanisms involving ADAMTS-7 in CAD remain elusive.

METHODS: We constructed a targeting vector for the genetic deletion of Adamts-7 using the insertion of a neomycin cassette and an IRES-sequence followed by the beta-Gal-gene, which leads to the interruption of the Adamts-7-reading frame. Successful knockout was confirmed by PCR and RT-PCR. Beta-galactosidase-activity was examined by X-Gal staining of various tissues in KO-mice and whole heterozygous embryos. To investigate neointima formation in WT- and KO-mice, carotid arteries (CA) were ligated and analyzed by histological staining. Contralateral carotid arteries were treated as sham controls.

RESULTS: Adamts-7-knockout-Mice were vital and appeared normal in growth and behavior. Using PCR and RT-PCR, the Adamts-7 gene was found to be interrupted by the neomycin cassette. X-gal staining demonstrated the correct insertion of the beta-Gal sequence and its expression under the influence of the Adamts-7-promoter. Remarkably, Adamts-7-knockout-mice remained resistant to proliferation of intima cells after CA ligation, whereas WT-mice showed marked neointima formation due to the injury.

CONCLUSION: Our Adamts-7-KO model has been shown to lack activity of functional Adamts-7. This seems to prevent these mice from developing intimal proliferation after CA ligation. The inhibition of ADAMTS-7 in humans may be a subsequent strategy for the prevention of neointima formation in patients at risk. Current studies focus on downstream signaling and pharmacological inhibition of ADAMTS-7.

Oral Presentation Abstracts

Symposium III

From Genomics to Application

From Genetic Research to Clinical Translation

Presenting Author: Cornelia van Duijn

Department of Epidemiology, Erasmus University Medical Center Rotterdam, NL

Genome wide association studies are rapidly uncovering an increasing number of loci involved in complex diseases. With some exceptions such as age related macular degeneration, for many traits including dyslipidemia and Alzheimer's disease, it remains difficult to predict risks for the future based on these common variants. At present, the utility of genome tests is limited, predominantly because they lack predictive ability and clear benefits for disease prevention that are specific for genetic risk groups. In the near future, personal genome tests will likely be based on whole genome sequencing, but will these technological advances increase the utility of personal genome testing? Whole genome sequencing theoretically provides information about the risks of both monogenic and complex diseases. Although new mutations with practical implications for families and individual carriers will be identified, the practical utility for the majority of patients with complex disease remains to be demonstrated. The utility of testing depends on the predictive ability of the test, the likelihood of actionable test results, and the options available for the reduction of risks. For monogenic forms of disease, it will be a challenge to recognize new causal variants among all rare variants that are found using sequencing. For complex diseases, the predictive ability of genetic tests will be mainly restricted by the heritability of the disease, but also by the genetic complexity of the disease etiology, which determines the extent to which the heritability can be understood. Given that numerous genetic and non-genetic risk factors may contribute to complex diseases, the predictive ability of genetic models will likely remain modest from a public health and clinical perspective. The major challenge for the near future will be to disentangle which complex diseases can be taken forward for (personal) genome testing.

A functional genomics scorecard predicts the quality and utility of human pluripotent cell lines for regenerative medicine

Presenting Author: Christoph Bock
Christoph Bock [1,2,3,5], Evangelos Kiskinis [2,5], Griet Verstappen [1,2,5], Hongcang Gu [1], Gabriella Boulting [2], Zachary D Smith [1,2], Michael Ziller [1,2], Gist F. Croft [4], Mackenzie Weygandt Amoroso [4], Derek H. Oakley [4], Andreas Gnirke [1], Kevin C Eggan [2], Alexander Meissner [1,2]

(1) Broad Institute of MIT and Harvard, Cambridge, MA, USA;

(2) Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA;

(3) Max-Planck-Institut für Informatik, Saarbrücken, Germany;

(4) Project A.L.S./Jenifer Estess Laboratory for Stem Cell Research, Columbia University, New York, NY, USA;

(5) equal contribution

The sustained proliferation and differentiation potential of human pluripotent stem cells suggests they could produce large quantities of disease-relevant cell types. However, substantial variation has been reported among pluripotent cell lines, which may affect their utility for disease modeling and transplantation therapy. Such cell-line specific differences must be better understood before we can confidently use embryonic stem (ES) or induced pluripotent stem (iPS) cells in translational research.
Towards this goal we have established a reference of 20 human ES lines and 12 human iPS cell lines that we characterized by genome-wide DNA methylation mapping, gene expression profiling and a novel high-throughput assay that quantifies differentiation propensities. We have applied this resource to quantify the epigenetic and transcriptional similarity of ES and iPS cells, and to predict cell-line specific responses to directed differentiation into neural and hematopoietic cells.
In summary, we found that epigenetic and transcriptional variation is common among human pluripotent cell lines and can have significant impact on a cell line's utility. This observation applies to both ES and iPS cell lines, underlining the need to carefully characterize each cell line, no matter how it was obtained. As a step toward lowering the experimental burden of comprehensive cell line characterization and to improve the accuracy over existing assays, we combined the three genomic assays into a bioinformatic scorecard that predicts the quality and utility of individual pluripotent cell lines.
Because the scorecard does not involve any labor-intensive steps, it becomes feasible to quickly screen through a large number of iPS cell lines in order to find the most appropriate cell lines for an intended application. Furthermore, the scorecard provides a substantially more detailed characterization than for example the teratoma assay.

High throughput copy number counting in single cells – a method for the detection of meiotic and mitotic errors

Presenting Author: Angelika Daser
Angelika Daser (1), Elizabeth Day (2), Heiko Turley (3), Anja Immesberger (3), Thomas Haaf (4), Ulrich Zechner (5), Thomas Hahn (1,3), Paul H. Dear (2), Martin Schorsch (1,3)

(1) SH-Gen Research, Wiesbaden, Germany

(2) MRC Laboratory of Molecular Biology, Cambridge, UK

(3) Fertility Center Wiesbaden, Wiesbaden, Germany

(4) University of Würzburg, Würzburg, Institute of Human Genetics, Germany

(5) University of Mainz, Mainz, Institute of Human Genetics, Germany

Clinical background is the low succes rate of pregnancies and baby take home rates after in vitro fertilisation techniques (IVF). Major reason is the high frequency of chromosomally abnormal (i.e. aneuploid) oocytes, exceeding 50% at 40 years. Selection of euploid oocytes is thus an attractive strategy to increase the number of live births following IVF.
The ploidy status of oocytes can be indirectly investigated by analysing the chromosome content in polar bodies (PB) I and II which are results of the first and second meiotic division before and after fertilisation; errors in meiotic divisions are due to chromosome non-disjunction and early sister chromatid separation. Therefore investigation of the chromosome content of PB I and II requires techniques which allow investigation of all chromosomes at the resolution of chromatids.
In contrast to microarray formats we count chromatids directly - molecular copy number counting (MCC) applied to a single cell, i.e. polar body. MCC is based on limiting dilution of the DNA to a concentration of less than one molecule of DNA per PCR reaction and digital PCR. The number of chromatids per chromosome is analysed by counting the numbers of positive PCR reactions representing target sequences on all chromosomes. To investigate all chromosomes with at least four markers (=96 markers) two rounds of specific PCR amplifications are required – a first round multiplex PCR containing all markers and a second, single marker PCR which is run on the BioMark system from Fluidigm. It provides a fast and convenient PCR system that allows to run and analyse 96 markers with 96 samples in less than 4 hours. Presence or absence of PCR products is analysed with melting curve analysis.
This method is simple and applicable to monitor not only meiotic but also mitotic cell divisions, copy number changes in general and to establish haplotypes for regions of interest in any given single cell.

The IT Future of Medicine – a flagship initiative to revolutionize our health care system

Presenting Author: Hans Lehrach
Hans Lehrach and Ralf Sudbrak on behalf of the ITFoM consortium

Max Planck Institute for Molecular Genetics, Berlin, Germany

Information Technology Future of Medicine (ITFoM) proposes to construct integrated molecular/physiological/anatomical models of every individual in the health care system, from baby to old age, as the basis of a data rich, computation intensive, individualised medicine of the future. The project plans to build on our current work on the use of genome and transcriptome data from tumor patients to construct virtual patient models able to predict effects and side effects of individual specific drugs or drug combinations on individual patients, but will extend this approach to many other data sources (many omics type techniques, imaging information, results from different types of sensors) as well as many other disease areas.
Such integrated molecular/anatomical models would, on one hand, offer the chance to develop a real individualised medicine, able to integrate the enormous amounts of data which can be expected to be generated in clinical diagnostics in the future. It would however also serve as an efficient interface for the doctor, since any doctor with experience in treating the real patient will have all the knowledge he needs to interact with the system.
In the past, innovation in ICT and computing has been primarily driven by the requirements of “large” physics and a broad spectrum of commercial applications such as entertainment. The growing demands of data-rich, individualised medicine are likely to surpass those of all other ICT development fields. As data-intensive analysis and computer intensive modelling become common clinical practice, ICT capacity and organization will become key limiting factors in medicine. This will result in a shift of resources from personnel-intensive to ICT-intensive applications. Clinical needs can therefore be expected to be the driving force behind future ICT innovation.

ITFoM is one of six shortlisted candidates, from which two will be chosen in 2013 as flagship projects under the EU Future and Emerging Technologies programme

Next steps in systemic analysis of mouse mutants at the German Mouse Clinic

Presenting Author: Martin Hrabé de Angelis
Martin Hrabé de Angelis (1,2), Helmut Fuchs (1), Valérie Gailus-Durner (1), Nina Offenhäuser (3), Klaus Strebhardt (4), the GMC consortium

(1) German Mouse Clinic, Institute of Experimental Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Ingolstaedter Landstrasse, 85764 Munich/Neuherberg, Germany

(2) Lehrstuhl für Experimentelle Genetik, TUM, Emil-Ramann-Strasse 8, 85350 Freising-Weihenstephan, Germany

(3) Fondazione Instituto FIRC di Oncologia Molecolare, Via Adamello 16. 20139 Milan. Italy

(4) Department of Obstetrics and Gynecology, School of Medicine, Johann Wolfgang Goethe-University, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany

The German Mouse Clinic (GMC) (www.mouseclinic.de) is a phenotyping platform with the logistics of systemic, standardized phenotypic analysis with open access for the scientific community on a collaborative basis. Since the launching of the NGFN the GMC has been an integral member of the network in the full exploitation of mutant mouse lines as models for human diseases. In the GMC I, mice are analyzed under resting conditions and the studies focus on the identification of alterations of basic organ and cell functions. In cooperation with clinicians from the clinical networks within NGFN-Plus we have phenotyped mutant lines as model systems for diseases such as Morbus Crohn and other inflammatory conditions, juvenile neuronal ceroid-lipofuscinosis, metabolic syndrom and we were able to discover new pathophysiological mechanisms. We will present data for the usage of inducible knockdown mouse lines such as the Plk1 iKD, which mimics the treatment of patients with anti-PLK1 drugs.
We have been setting up challenge platforms (GMC II) to explore the complex relationship between environmental influences and genetic factors. By exposing mutant mice to specific and standardized environmental situations (envirotypes) such as nutrition, activity, air, infection and stress, we mimic human life stiles and their impact on human health. Our goal is to decipher the effects of different envirotypes on disease etiology and progression, uncovering the physiological and molecular mechanisms of genome-environment interactions. We will present examples from selected mutant mouse lines, such as Eps8 that are deficient in the regulator of actin dynamics Eps8 with resistance to diet-induced obesity.
Recently we have started to implement the GMC III, a platform for the systemic analysis of compounds and drugs. Data from a pilot project will be presented.

The BLUEPRINT of hematopoiesis

Presenting Author: Henk Stunnenberg

Nijmegen Centre for Molcular Life Sciences,Nijmegen, NL

The regulation of gene expression is paramount in growth, development, differentiation, signaling, adaptation to the environment and many other processes. Gene expression is regulated at many levels, but primarily by binding of specific transcription factors to regulatory regions, resulting in the recruitment of activating or repressive factors and subsequent changes in mRNA levels and gene activity. Identification of the target gene and binding site networks of transcription factors is vital to understand its role. The application of massively parallel sequencing to ChIP (ChIP-Seq) has opened up new avenues at the genome-wide scale to elucidate entire regulatory networks and pathways. The increasing sequence capacity enables for the first time the genome wide identification and integration of transcription factor binding sites, histone marks, DNA methylation as well as RNA polymerase II occupancy and quantitative transcriptome sequencing (RNA-seq) at different time points, conditions and cell lines. I will discuss our 'epigenetic/systems' biology approach to gain molecular insight into the action of oncofusion proteins in Acute Myeloid Leukaemia.

Future Medicine: The promise and challenge of translating science into health care

Presenting Author: Klaus Lindpaintner

SDIX (Strategic Diagnostics Inc.), Newark, Delaware, USA

Recent decades have seen impressive progress in our understanding of basic cell biology in health and disease and, as a consequence, we are witnessing the emergence of a new taxonomy of medicine that holds tremendous promise for more targeted approaches to treating, and perhaps even preventing illness. In parallel, although slower, encouraging advances are taking place in translating some of this knowledge into clinically actionable changes in disease management that have started to impact patient care. Meanwhile, challenges related, in part, to historically rooted, parochial boundaries between disciplines as well as between participating parties in the health science and provision sectors remain, impeding optimal leverage of scientific progress into improving clinical practice. Given the even greater and daunting societal and economic challenges that the future of health care provision on both national and global levels faces – in part, ironically, because of the scientific progress made—we can ill afford such inefficacies, and it is imperative that we work diligently to overcome these boundaries.

National Genome
Research Network

Oral Presentation Abstracts

Symposium IV
Genomics of Infection, Inflammation & Environmental Interaction

Impact of the immune system on metastatic breast cancer and chemotherapy efficacy

Presenting Author: Karin E. de Visser
Metamia Ciampricotti(1), Tisee Hau(1), Chris W. Doornebal(1), Svenja Debey-Pascher(2), Joachim L. Schultze(2), Jos Jonkers(1), Karin E. de Visser(1)

(1) Division of Molecular Biology, Netherlands Cancer Institute, Amsterdam, The Netherlands

(2) Genomics and Immunoregulation, LIMES (Life and Medical Sciences Bonn), University of Bonn, Germany

Whereas it has become generally accepted that chronic activation of innate immune cells contributes to cancer development and metastasis formation, the role of the adaptive immune system during tumorigenesis, metastatic disease and response to chemotherapy is still a matter of debate. Both tumor-protective and tumor-promoting properties of the adaptive immune system have been described in clinical and experimental settings. The overall goal of our research is to address the impact of the adaptive and innate immune system on de novo metastatic breast cancer and chemotherapy efficacy. We utilize two transgenic mouse models that develop spontaneous mammary carcinomas, i.e. MMTV-NeuT mice and K14cre;EcadF/F;p53F/F mice. These mouse models develop metastatic mammary carcinomas that resemble human HER2+ breast cancer and human invasive lobular carcinomas respectively. Like human breast cancers, mammary carcinomas arising in these mice are characterized by abundant influx of innate and adaptive immune cells and increased levels of pro-inflammatory mediators. We examined the functional significance of the adaptive immune system as a regulator of metastatic breast cancer and chemotherapy response in both mouse tumor models. Interestingly, our findings suggest that distinct subtypes of metastatic breast cancer are differently modulated by the adaptive immune system. These findings correlate with an impact of the adaptive immune system on the gene expression profile of tumor-associated macrophages. We are currently assessing the underlying mechanisms by which the adaptive immune system promotes metastasis formation. Ultimately, the outcome of these studies may shift therapeutic focus from a cancer cell intrinsic point of view towards a more combined cancer cell intrinsic and extrinsic point of view (Funded by the Dutch Cancer Society grants 2006-3715 and 2011-5004, NWO/VIDI 91796307 and AICR 11-0677).

Impaired host-microbiome crosstalk in inflammatory bowel disease

Presenting Author: Robert Häsler
Robert Häsler (1), Patricia Lepage (1,4), Martina E Spehlmann (1), Ateequr Rehman (1), Aida Zvirbliene (3), Alexander Begun (1), Stephan Ott (1,5), Limas Kupcinskas (3), Joël Doré (4), Andreas Raedler (2) and Stefan Schreiber (1,5)

(1) Institute of Clinical Molecular Biology, Christian-Albrechts University – Kiel, 24105 Kiel, Germany

(2) Department of Internal Medicine, Asklepios Westklinikum Hamburg, Hamburg, Germany

(3) Department of Gastroenterology, Kaunas University of Medicine, 44307 Kaunas, Lithuania

(4) INRA, UMR1319, MICALIS, 78350 Jouy-en-Josas, France

(5) Department of Internal Medicine I, Christian-Albrechts-University – Kiel, 24105 Kiel, Germany

Environmental factors in combination with genetic susceptibility are currently being discussed as major drivers contributing to manifestation and progression of inflammatory bowel disease, such as ulcerative colitis (UC). One aspect of this interaction with the environment is the host-microbiome crosstalk.
Here we systematically quantify host-microbiome interaction by correlating bacterial signals originating from 16S rDNA libraries with mRNA signals originating from genome-wide transcriptome analysis. To minimize genotype effects on the microbiome, this was examined in the primary mucosa of monozygotic twins, discordant for UC. In addition to the diseased individuals and their healthy siblings, healthy unrelated individuals were included in the study.
Combining the bacterial profile with the transcriptome displayed significant differences between UC patients, their healthy siblings and healthy unrelated individuals: Healthy unrelated individuals showed 34 interaction-signals, healthy siblings of UC patients showed 25 interaction-signals while UC patients showed only 11 interaction-signals. These differences are significantly higher than expected by chance (false discovery rate < 5%).
Our results show an interaction of the human colonic mucosa with its microbiota. The butyrate production of some of the identified bacterial genera may potentially influence mucosal gene expression. The host-microbiome interaction is significantly decreased in UC patients when compared to their healthy siblings and decreased even further when compared to healthy unrelated individuals. This indicates a potentially disease associated effect, where the healthy siblings of UC patients may represent a pre-disease-manifestation status. Understanding the interplay between host genetics, host pathophysiology and gut microbiota, which represent three key elements in UC, will help to progress towards the development of new diagnostic and therapeutic strategies.

Integrative data analysis of cancer tissues using next generation sequencing

Presenting Author: Martin Kerick
Ole Eigenbrod (1), Martin Kerick (1), Axel Fischer (1), Stephan Börno(1), Bernd Timmermann (2), Uta Marchfelder (1), Hans Lehrach (1), Andreas Dahl (3) and Michal-Ruth Schweiger (1)

(1) Max Planck Institute for molecular Genetics - Berlin, Department Vertebrate Genomics

(2) Max Planck Institute for molecular Genetics - Berlin, Next Generation Sequencing Center

(3) Biotechnology Center TU - Dresden, Deep Sequencing Group - SFB655

High-throughput sequencing technologies have brought the possibility to systematically investigate genomes and epigenomes of complex genetic diseases. Hope arises that in the future it will be possible to shed light on the interconnection between different cellular levels and thus to get hold on the underlying pathomechanisms. In particular for cancer large-scale analyzes are being performed and correlations with disease states extracted. The investigation of genomic features like methylation patterns, copy number variations or transcriptomic activity has led to the development of analysis techniques which, however, most often address only one of these datasets.
In this study we have explored the potential of data integration and we combined whole genome SOLiD sequencing, MeDIP-seq and RNA-seq data of the colorectal cancer cell lines model – the tumor cell line SW480 and the corresponding metastasis SW620 line. We present data on the relation of strand- and allele-specific cytosine methylation, gene expression, mutations and copy number variations. Furthermore, we have extended the models from cell lines to primary tissue material and demonstrate the universality of our approach.

Early detection of colorectal cancer from patient blood plasma using microRNA-based RT-qPCR

Presenting Author: Adam Baker
Roman Kurek (1), Søren J. Nielsen (1), Nana Jacobsen (1), Jacob U. Fog (1), Hanni Willenbrock (1), Jan Stenvang (5), Torben F. Ørntoft (2),Nils Brünner (5), Hans J. Nielsen (3), Claus L. Andersen (4), Adam Baker (1)

(1) Exiqon A/S, Vedbaek, Denmark

(2) Department of Molecular Medicine (MOMA), Aarhus University Hospital, Aarhus, Denmark

(3) Department of Surgical Gastroenterology, Hvidovre Hospital, Hvidovre, Denmark

(4) Department of Molecular Medicine (MOMA) and Department of Surgery (THG), Aarhus University Hospital, Aarhus, Denmark

(5) Department of Veterinary Disease Biology, University of Copenhagen, Frederiksberg C, Denmark

A large number of studies have demonstrated a causal link between microRNA dys-regulation and numerous diseases including a diverse array of human cancers. The high relative stability of microRNA in common clinical source materials (e.g. FFPE, plasma, serum, urine, etc.) has furthermore positioned microRNA quantification as a promising new tool for a wide range of diagnostic applications.
To facilitate discovery of microRNA-based diagnostic markers, we developed a genome-wide LNA™-enhanced microRNA qPCR platform which facilitates detection of microRNAs even from challenging clinical sources. The platform uses a universal RT system and thus allows high-throughput genome-wide profiling of microRNAs from clinical sources without the need for pre-amplification.
Using this system, we have studied plasma microRNAs for early detection of colorectal cancer (CRC). We have profiled a large amount of plasma samples from CRC patients and matched healthy controls in search of microRNA biomarkers. The LNA™- enhanced microRNA qPCR platform not only showed unparalleled sensitivity and robustness for detection of microRNA in challenging clinical source material but also allowed us to accurately define microRNAs that are differentially expressed in the plasma of healthy volunteers versus CRC patients. The result is a clinically viable and feasible approach for minimally invasive early detection of CRC.

IG Cellular Systems Genomics: Network analysis of tumor drug resistance

Presenting Author: Stefan Wiemann
Stefan Wiemann (1), Dorit Arlt (1), Stephanie Bechtel (1), Tim Beißbarth (1), Anne-Claude Gavin (2), Anika Jöcker (1), Ulrike Korf (1), Bodo Lange (3), Rainer Pepperkok (2), Annemarie Poustka (1), Heiko Rosenfelder (1), Özgür Sahin (1), Andreas Schneeweiss (4), Ulrich Tschulena (1)

(1) Deutsches Krebsforschungszentrum - Heidelberg, Division Molecular Genome Analysis

(2) European Molecular Biology Laboratory - Heidelberg, Cell Biology and Biophysics and Structural and Computational Biology Units

(3) Max Planck Institute for Molecular Genetics - Berlin, Department of Vertebrate Genomics

(4) University Clinics and National Center for Tumor Diseases - Heidelberg

The IG-Cellular Systems Genomics combines high-throughput reverse genetic screening approaches with quantitative proteomics and cell biology technologies to unravel mechanisms of drug resistance in cancer treatment. Our initial focus is on breast cancer, where the ERBB-signaling network is known to be causally related to disease progression. We perform systematic screening for novel components of relevant signaling pathways and validate findings via protein interaction mapping. Since the observed cross-talk between individual signaling pathways is not only via protein interactions, we extend on the impact miRNAs, epigenetic changes and mutations have in order to also cover longer term effects.
The comprehensive analysis of ERBB-signaling, initially in cell-line models and then in patient samples, gives us an integrated view on the impact this signaling network has in breast cancer, and lays the ground for a better understanding of the molecular mechanisms leading to disease, resistance and metastasis. This directs us towards systems genomics models that predict and validate novel markers for diagnosis and prognosis as well as target molecules with potential for therapeutic intervention.

Oral Presentation Abstracts

Symposium V

Genomics of Cancer

Human Induced Pluripotent Stem Cells Harbor Homoplasmic and Heteroplasmic Mitochondrial DNA Mutations While Maintaining Human Embryonic Stem Cell-like Metabolic Reprogramming

Presenting Author: Alessandro Prigione
Alessandro Prigione (1), Björn Lichtner (1), Heiner Kuhl (2), Eduard A. Struys (3), Mirjam Wamelink (3), Hans Lehrach (1), Markus Ralser (1), Bernd Timmermann (2), James Adjaye (1,4)

(1) Department of Vertebrate Genomics, Max Planck Institute for Molecular Genetics, 14195 Berlin, Germany.

(2) Next Generation Sequencing Group, Max Planck Institute for Molecular Genetics, 14195 Berlin, Germany.

(3) Department of Clinical Chemistry, Metabolic Unit, VU Medical Center, de Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.

(4) The Stem Cell Unit, Department of Anatomy, College of Medicine, King Saud University, Riyadh, 11461, Saudi Arabia.

Human induced pluripotent stem cells (iPSCs) have been recently found to harbor genomic alterations. However, the integrity of mitochondrial DNA (mtDNA) within reprogrammed cells has yet to be investigated. mtDNA mutations occur at a high rate and are believed to contribute to the pathology of a number of human disorders. Furthermore, the lack of mtDNA integrity may alter cellular bioenergetics and limit efficient differentiation. We previously demonstrated that the derivation of iPSCs is associated with mitochondrial remodeling and a metabolic switch towards glycolysis. Here, we have discovered that alterations of mtDNA can occur upon the induction of pluripotency. Massively parallel pyrosequencing of mtDNA revealed that human iPSCs derived from young healthy donors harbored single base mtDNA mutations (substitutions, insertions, and deletions), both homoplasmic (in all mtDNA molecules) and heteroplasmic (in a fraction of mtDNAs), not present in the parental cells. mtDNA modifications were mostly common variants and not disease-related. Moreover, iPSC lines bearing different mtDNA mutational loads maintained a consistent human embryonic stem cell-like reprogramming of energy metabolism. This included over-expression of glycolytic enzymes, increased amount of glucose-6-phosphate, and elevated protein expression of pyruvate dehydrogenase kinase 1, which re-routes the bioenergetic flux toward glycolysis. Hence, mtDNA mutations within iPSCs may not necessarily impair the correct establishment of pluripotency and the associated metabolic reprogramming. Nonetheless, the occurrence of pathogenic mtDNA alterations might be an important aspect to monitor when characterizing iPSC lines. Finally, we speculate that this random re-arrangement of mtDNA molecules might prove beneficial for the derivation of mutation-free iPSCs from patients with mtDNA disorders.

Development of molecular inhibitors targeting hot spots of AML1/ETO dimer-tetramer transition

Presenting Author: Christian Wichmann
Christian Wichmann (1), Julia Schanda (1) & Manuel Grez (1)

(1)Georg-Speyer-Haus, Institute for Biomedical Research, Frankfurt am Main, Germany

Chromosomal translocations are frequent events during malignant cell transformation, particularly in leukemogenesis. The translocation t(8;21), one of the most frequent chromosomal anomaly in leukemia, involves the AML1 gene on chromosome 21 and the ETO gene on chromosome 8. Essential for the transforming abilities of AML1/ETO is the oligomerization of AML1/ETO proteins. We could show that expression of a polypeptide targeted to the tetramer domain of AML1/ETO, disrupts oligomerization, restores expression of AML1/ETO target genes and reverses the block in myeloid differentiation. Our data propose the oligomerization domain of ETO as a promising target structure for a molecular intervention in AML1/ETO leukemias.
We further analyzed the energetic contribution of individual amino acid side chains within the NHR2 domain to AML1/ETO dimer-tetramer transition and found a clustered area of five distinct amino acids with strong contribution to the stability of tetramers. Substitution of these five amino acids abolishes tetramer formation without affecting dimer formation. AML1/ETO dimers failed to bind to DNA and to alter expression of AML1-dependent target genes. AML1/ETO dimers do not block myeloid differentiation, are unable to enhance the self-renewal capacity of hematopoietic progenitors and fail to induce leukemia in a murine transplant model. These data reveal the existence of an essential structural hot spot at the NHR2 dimer-tetramer interface, suitable for a molecular intervention.
To test this concept, we derived several 18-mer peptides addressing different areas on the AML1/ETO dimer interacting surface. Interestingly, the 18-mer peptide which addresses the hot spot region shows the strongest inhibitory effect on tetramer formation in a dose depended manner. This 18-mer peptide now serves as a lead structure for the development of small molecule inhibitors addressing the dimer-tetramer hotspot and thereby targeting AML1/ETO's oncogenic function.

miRNAs in prostate cancer

Presenting Author: Ruprecht Kuner
Ruprecht Kuner (1), Jan C. Brase (1), Daniela Wuttig (1), Marc Johannes (1), Stephan Gade (1), Jenny Metzger (1), Thorsten Schlomm (2), Maria Fälth (1), and Holger Sültmann (1)

(1) Working group Cancer Genome Research, German Cancer Research Center and National Center for Tumor Diseases, Heidelberg, Germany;

(2) Martini-Clinic, Prostate Cancer Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

miRNAs are short (19-26 nucleotides) RNA molecules, which have been suggested to be regulators of biological functions. Alterations in miRNA expression can affect vital cellular processes like cell cycle, proliferation, or apoptosis, thus providing a direct link to cancer development and progression. In an effort aiming at the identification and validation of molecular parameters for the stratification of prostate cancer, one of the major causes of tumor death in males, we have performed global screenings for 667 miRNAs.
In a comparison between prostate tumor and normal tissues (N=92), we identified a large set of differentially expressed miRNAs and correlated these with the global gene expression patterns obtained from the same samples. A clear miRNA expression signature was associated with malignancy. Furthermore the expression of several miRNAs was associated with tumor grade. By transfection of a selected subset of miRNA mimics into prostate cancer cells, we determined their in vitro functional effects and provided associated cellular processes and downstream targets.
The unique stability of miRNAs renders them potentially useful for detection in a variety of patient samples, including FFPE tissue or body fluids. In order to evaluate the potential of a low invasive diagnosis of tumors, we performed miRNA expression analysis in serum samples of prostate cancer patients. In a screening study, followed by an independent validation cohort in prostate cancer, we found several serum miRNAs to be associated with lymph node metastasis (N=137). Although these data have to be further corroborated using larger independent sample cohorts, our findings (and those of other researchers) indicate the utility of serum miRNA abundance for the diagnosis and prognosis of prostate cancer.

Affinity-based proteomic analysis of pancreatic cancer

Presenting Author: Jörg D. Hoheisel
Christoph Schröder (1), Mohamed Saiel Saeed Alhamdani (1), Andrea Bauer (1) and Jörg D. Hoheisel (1), Nathalia Giese (2), Jens Werner (2) and Markus Büchler (2)

(1) Division of Functional Genome Analysis, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 580, Heidelberg, Germany

(2) Department of Surgery, University of Heidelberg, Im Neuenheimer Feld 110, Heidelberg, Germany

Background: Pancreatic adenocarcinoma is one of the most aggressive and malignant tumour entities; mortality is nearly identical to incidence. Most patients die within a year of diagnosis. The poor prognosis is caused by the lack of both appropriate markers for early diagnosis and effective treatment options for the late stages that are consequently seen in clinics.

Methods: In an effort to develop means for early and accurate diagnosis and for an understanding of functional molecular aspects of the disease, we have performed proteome studies by means of a complex antibody microarray with some 1000 binders. We also compared the results to data sets produced from the very same samples at the levels of mRNA, microRNA and promoter methylation.

Results: For early diagnosis, several hundred urine and serum samples were analysed, yielding diagnostic protein patterns of high accuracy and specificity. Also, variations in the protein abundance and structure of 650 tissue samples were studied, using also antibody pairs that are specific for either the wildtype protein or a cancer-associated isoform. Last, 24 pancreatic cancer cell lines and appropriate controls were investigated. Next to an analysis of the mere differences of their cellular proteomes, we also induced the cells by addition of various factors such as interferons and measured the resulting variations in the secretome.

Conclusions: The study revealed many new characteristics of the disease including, for example, information about its degree of differentiation, the source of cells and the metastatic potential. The results form the basis for non-invasive and early diagnosis, allow a molecular assessment, such as more accurate grading of the disease and a determination of its metastatic potential. Protein isoforms were revealed that are specific for tumour tissues and have strong relevance to therapy.

www.dkfz.de/funct_genome/

Multiple (epi)genetic modifier loci of Apcmin-induced tumourigenesis identified using chromosome substitution strains

Presenting Author: Alexandra Farrall
Alexandra Farrall(1), Christina Grimm(2), Markus Morkel(1), Lukas Chavez(2), Ralf Herwig(2), Hans Lehrach(2), Bernhard Herrmann(1)

(1) Department of Developmental Genetics, Max Planck Institute for Molecular Genetics, Berlin, Germany

(2) Department of Vertebrate Genomics, Max Planck Institute for Molecular Genetics, Berlin, Germany

Inactivating mutations of APC occur in 70-80% of sporadic colorectal cancers and are causative for familial adenomatous polyposis (FAP) in humans. The Apcmin mouse model of FAP has provided insight into the genetic networks underlying intestinal tumourigenesis, and is widely used to study the impact of genetic variation on the disease phenotype. In humans, where disease susceptibility is polygenic and complex, the influence of the individual genetic background on the lifetime risk of developing cancer and/or prognosis remains to be fully understood. To study disease susceptibility in a well-defined genetic model, we set up a screen to identify novel modifiers of the Apcmin-induced tumour phenotype using chromosome substitution strains (CSS), which carry single chromosomes of the PWD/Ph strain on a C57BL/6 (B6) background. Multiple B6/CSS F1 strains displayed reduced tumour-burden, indicating the existence of multiple modifiers on different chromosomes. To identify modifier loci we used high density SNP analysis to direct back-cross breeding of subcongenic lines. At present we have identified loci on chromosomes 3 and 5, both of which appear to function in a dosage-dependent manner. Since a focus of our program to identify modifiers of epigenetic regulation and tumour progression, we also studied global changes in the epigenetic and transcriptional landscapes during tumour initiation in B6 and C5 subcongenic animals. Ongoing analyses already reveal genome-wide sets of modified loci during oncogenic transformation of intestinal tissue that change upon introduction of PWD C5. We employ 3D organotypic culture systems of the normal and the transformed intestinal epithelium to link changes in the epigenome to gene expression, and for future functional validation studies of putative modifiers. Combining these approaches will allow us to isolate key (epi)genetic modifiers involved in intestinal cancer initiation, stem cell function, and disease progression.

Cancer Genome Analysis in Chronic Lymphocytic Leukemia

Presenting Author: Ivo G. Gut

Centro Nacional de Análisis Genómico, Barcelona, Spain

The International Cancer Genome Consortium (ICGC) aims to fully characterize in the 50 most common forms of cancer 50 tumour/normal sample pairs exhaustively and then to validate observations in further 450 samples. The first two years of this project have seen huge advances in the development, implementation and standardisation of the methods for characterising samples, ethical approval, whole-genome sequencing, exome sequencing, RNA sequencing, epigenetic analysis, methods for validation, informatics analysis and data basing.
The Spanish contribution to the ICGC is on Chronic Lymphocytic Leukaemia (CLL). Our main responsibility has been on whole genome sequence analysis, exome analysis, RNA sequence analysis and epigenetic analysis. Complete genome sequencing of many samples requires bringing together many different elements, starting from samples, preparation for sequencing, sequencing itself, data analysis, through to verification of results and translating a result into biological knowledge. Thorough examination of the first batches of complete molecular characterisations and follow up in a large replication set allowed us to identify four recurrent in the NOTCH1, XPO1, MYD88 and the KLHL6 genes. Interestingly the two recognised subtypes of CLL, immunoglobulin modulated and not, do not completely reflect themselves in the recurrent mutations. The methods and findings will be discussed.

Poster Presentation Abstracts

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Symposium I

Genomics of CNS Disorders

Animal Models for Risk Genes of Alzheimer's Disease

Presenting Author: Thomas Floss
Thomas Floss (1), Anke Wittmann (1), Matthias Riemenschneider (2), Marcus Grimm (3), Tobias Hartmann (3) and Wolfgang Wurst (1)

(1) Institute of Developmental Genetics, Helmholtz Zentrum München, National Research Center for Enviroment and Health, Ingolstädter Landstr. 1, 86574 München-Neuherberg

(2) Dept. of Psychiatry and Psychotherapy, Universitätsklinikum des Saarlandes, 66421 Homburg/Saar

(3) Deutsches Institut für Demenzprävention (DIDP), Institute for Neurodegeneration and Neurobiology Research, Neurology, Medical Campus of the Saarland University, Kirrbergerstr. Building 61.4, 66421 Homburg

Dementias represent the most cost-intensive burdens of our health system. In our ageing society, the number of affected individuals is expected to double from 1 to 2 Mio. within the next 20 years. Yet, age-dependent dementias are not understood and early diagnosis or slowing of disease-progression is not available. The Goal of this IG is to functionally validate new candidate genes identified in GWAS screens or by other means, that are associated with Alzheimer's disease (AD) by using mouse models. In particular, here we focus on recently identified genes involved in lipid metabolism. Functional analysis of these mouse models includes behavioural, neuroanatomical and molecular genetic methods as well as environmental challenges. This approach will validate determinants of AD identified within this IG and provide models that closely meet clinical expectations and demands. Therefore, our work program significantly contributes to the understanding of the underlying pathophysiology and molecular causes of Alzheimer's disease. The models themselves and all cellular systems derived from these models (e.g. mouse embryonic fibroblasts, astrocytic and neuronal cultures) for further biochemical and molecular analysis will be available to all other subprojects.

German Mouse Clinic - environmental influences on neuropsychiatric diseases

Presenting Author: Lillian Garrett
Lillian Garrett (1,3), Annemarie Wolff-Muscate(1,3), Alexander Mayer (1), Martin Hrabe de Angelis (3), Jan Deussing (4), Wolfgang Wurst (1,2), Sabine M. Hölter (1,3)

(1) Institute of Developmental Genetics, (3) German Mouse Clinic, Helmholtz Zentrum München – German Research Center for Environmental Health, D-85764 Munich, Germany

(2) Technical University Munich, Germany

(4) Max Planck Institute of Psychiatry, Kraepelinstr, 2-10, 80804 Munich, Germany

A scientific interest of the German Mouse Clinic Behavioural Screen is the effect of lifestyle on the progression of disease. Chronic stress is a risk factor for the development of neurodegenerative disease whereas exercise can be protective. In this context, adult neurogenesis may play a role, since chronic stress reduces adult neurogenesis, and neurogenesis is reduced in neurodegenerative disease. Exercise mitigates symptoms of stress and anxiety, in addition to increasing neurogenesis in rodents. To study these interactions, we established acute and chronic stress protocols for use in mice and a wheel-running paradigm. Restraint is the stressor of choice that effectively mimics psychosocial stress in man. The acute stress protocol can be used to evaluate both hypo- and hyper-reactive mice using different restraint periods followed by the Open Field Test. The influence of two durations of voluntary running wheel access (14 days vs. 28 days) as well as the effect of the combination of exercise and chronic restraint stress on measures of neurogenesis is presented. Ultimately, we will use this stress challenge/wheel running paradigm to look at the effects of exercise on stress coping and disease development in genetic mouse models of neurodegenerative diseases. The marriage of the stress platform with voluntary exercise will provide innumerable possibilities for elucidating the more complex and inducible phenotypes of mutant mouse models that may be extrapolated to the human disease condition.

Behavioural phenotypes in genetic mouse models of Parkinson’s Disease

Presenting Author: Lisa Glasl
L. Glasl (1), F. Giesert (1), K. Kloos (1), U. Hafen (1), A. Hofmann (1), J. Graw (1,2), N. Prakash (1), M. Rosemann (3), L. Becker (2), T. Klopstock(2), D.M. Vogt Weisenhorn (1), M. Hrabé de Angelis (2), W. Wurst (1,2), S.M. Hölter (1,2)

(1) Institute of Developmental Genetics,

(2) German Mouse Clinic,

(3) Department of Radiation Sciences; Helmholtz Zentrum München

Parkinson’s disease, as the second most common neurodegenerative disorder, is age-related and in most cases, the etiology of the disease is unknown. However, there is a well-established genetic component in a considerable subset of patients and several distinct loci, including mutations in Pink1, DJ1, Lrrk2 and α-Synuclein (Snca), which have been implicated in rare familial forms. The majority of the PD cases appear to be sporadic, but associations with polymorphic sites in the Pitx3 gene were found in epidemiological studies and contribute to the susceptibility to PD (Fuchs et al., 2009). The discovery of the specific familial genes led to the development of novel genetic mouse models. Intriguingly, none of the mouse models for familial forms reproduces the major hallmark of PD that is the loss of dopaminergic neurons in the substantia nigra, although, all three mouse lines deficient for Pitx3 show this. We investigated all these PD mouse models systematically at different ages, using a comprehensive behavioral test battery encompassing motor, cognitive and olfactory phenotypes. Our study revealed that the genetic mouse models for familial forms of PD (Pink1, DJ-1; Lrrk2, and Snca) exhibit important symptoms of the early phase of PD, like gait impairments as well as gene- but not age-related non-motor symptoms such as olfactory deficits. In contrast, mouse lines deficient for Pitx3 showed motor features of the late phase of PD, consistent with their reductions of dopaminergic neurons in the substantia nigra.

Smad interacting protein 1 modulates thermal, but not mechanical pain

Presenting Author: Ildikó Rácz
B. Pradier1*, M. Jeub2, A. Markert1, D. Mauer1, V. Gailus-Durner3, H. Fuchs3, M. Hrabé de Angelis3, D. Huylebroeck4, H. Beck2, A. Zimmer1,3, I. Rácz1,3

(1) Institute of Molecular Psychiatry, University of Bonn, Germany

(2) Laboratory for experimental epileptology, University of Bonn, Germany

(3) German Mouse Clinic, Helmholtz-Zentrum, Munich, Germany

(4) Laboratory of Molecular Biology (Celgen), Department of Molecular and Developmental Genetics, Flanders Institute of Biotechnology, Leuven, Belgium

Smad-interacting protein-1 (Sip1, Zfhx1b) is a transcription factor that plays an important role in neuronal development and is involved in the aetiology of the Mowat-Wilson Syndrome. A corresponding mouse model carrying a heterozygous Zfhx1b deletion was comprehensively analyzed in the German Mouse Clinic. The most prominent phenotype was a reduced pain sensitivity.
In this study we investigated the Zfhx1b heterozygous animals in models of acute and chronic pain. To examine the nociceptive transmission of primary sensory dorsal root ganglia (DRG) neurons we determined the neuronal activation upon painful stimulation in the spinal dorsal horn. Next, we characterised the neuronal cell population in DRGs to study the involvement of the Zfhx1b mutation in peripheral nociception.
The present data show that Zfhx1b is involved in the development of primary sensory DRG neurons, especially of C- and A δ-fibres. These alterations contribute to a hypoalgesic phenotype in heterozygous Zfhx1b mice. Further, the transcription factor modulates peripheral sensitisation of thermal and chemical nociceptors under acute and formalin-induced pain conditions.

Testing the glutamate theory of alcohol addiction in humans

Presenting Author: Rainer Spanagel
Valentina Vengeliene (1)*, Gerhard A. Wiesbeck (2)*, Fernando Leonardi-Essmann (1), Oliver Stählin (1), Wolfgang H. Sommer (1), Wojciech Danysz (3), Chris G. Parsons (3), Michael Althaus (3), Roberto Ciccocioppo (4), Petri Hyytiä (5), Markus Heilig (6), Donna Sheedy (7), Clive Harper (7), Jobst Böning (8), Karl Mann (9), Rainer Spanagel (1)

*** Equal contribution**

(1) Institute of Psychopharmacology, Central Institute of Mental Health, Mannheim, Germany

(2) Psychiatric Hospital, University of Basel, Switzerland

(3) Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany

(4) Department of Pharmacological Science and Experimental Medicine, University of Camerino, Italy

(5) National Public Health Institute, Helsinki, Finland

(6) Laboratory of Clinical and Translational Studies, NIAAA, National Institutes of Health, Bethesda, USA

(7) Discipline of Pathology, University of Sydney, Australia

(8) Clinic for Psychiatry, Psychosomatic Medicine and Psychotherapy, University of Würzburg, Würzburg, Germany

(9) Clinic of Addiction Medicine, Central Institute for Mental Health, Mannheim, Germany

The glutamate theory of alcohol addiction is the most prominent theory in the alcohol research field. Consequently, compounds acting at different glutamate receptors are currently being developed by pharmaceutical companies. Given that the novel NMDA receptor (NMDAR) channel blocker neramexane diminished alcohol relapse in an animal model we have tested this compound in humans. In a multicentre trial, neramexane was tested against placebo in detoxified alcohol-dependent subjects. Patients were randomised to either the neramexane group (n=117; 2 x 20 mg per day) or the placebo group (n=119). After 12 weeks of double-blind treatment, 25% of the neramexane treated patients compared to 31% placebo controls remained continuously abstinent. Using further animal studies and post-mortem brain tissue from deceased alcoholics we found alterations in NMDAR subunit composition that might explain the lack of effect of neramexane in our phase II study. Thus NMDARs composed of NR1/NR3A subunits exhibit reduced sensitivity to channel blockers compared with NR1/NR2A receptors. Indeed when we co-expressed the NR3 subunit with human NR1/2A receptors we observed a dramatically reduced response to neramexane. We concluded that neramexane may only act as an effective treatment when high doses are administered. Hence we performed a post-hoc analysis on neramexane plasma levels and abstinence duration and found that patients with neramexane plasma levels above 20 ng/ml had a significantly higher rate of continuous abstinence after 12 weeks of treatment than placebo patients. Neramexane given at high doses prevents relapse – a finding in humans that is in line with the glutamate theory of alcohol addiction.

GWAS, Pathway and Score Based Analysis of Alcohol Dependence

Presenting Author: Josef Frank
Josef Frank (1), Jens Treutlein (1), Monika Ridinger (5), Manuel Mattheisen (2,6,7), Per Hoffmann (2,3), Stefan Herms (2,3), Norbert Wodarz (5), Michael Soyka (8,9), Peter Zill (9), Wolfgang Maier (10), Rainald Mössner (10), Wolfgang Gaebel (11), Norbert Dahmen (12), Norbert Scherbaum (13), Christine Schmäl (1), Michael Steffens (6), Susanne Lucae (14), Marcus Ising (15), Dilafruz Juraeva (16), Benedikt Brors (16), Bertram Müller-Myhsok (17), , Karl Mann (18), Falk Kiefer (18), Markus M. Nöthen (2,3), Sven Cichon (2,3,4), Marcella Rietschel (1)

(1) Dept. of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, (2) Dept. of Genomics, Life & Brain Center, Univ. of Bonn, (3) Inst. of Human Genetics, Univ. of Bonn, (4) Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, (5) Dept. of Psychiatry, University Medical Center Regensburg, Univ. of Regensburg, (6) Inst. for Medical Biometry, Informatics, and Epidemiology, Univ. of Bonn, (7) Department of Biostatistics, Harvard School of Public Health, (8) Private Hospital Meiringen, (9) Dept. of Psychiatry, Univ. of Munich, (10) Dept. of Psychiatry, Univ. of Bonn, (11) Dept. of Psychiatry and Psychotherapy, Univ. of Düsseldorf, (12) Dept. of Psychiatry, Univ. of Mainz, (13) Addiction Research Group at the Department of Psychiatry and Psychotherapy, LVR Hospital Essen, University of Duisburg-Essen, (14) Dept. of Psychiatric Pharmacogenetics, Max-Planck-Institute of Psychiatry, Munich, (15) Dept. of Molecular Psychology, Max-Planck-Institute of Psychiatry, Munich, (16) Div. Theoretical Bioinformatics, German Cancer Research Center, Heidelberg, (17) Dept. of Statistical Genetics, Max-Planck-Institute of Psychiatry, Munich, (18) Dept. of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health

Background: Alcohol dependence (AD) is an important contributing factor to the global burden of disease. The etiology of AD involves both environmental and genetic factors and the disorder has a heritability of around 50%. The aim of the present study was to identify susceptibility genes for AD by performing a genome-wide association study (GWAS).
Methods: Genotyping was performed in 900 patients. Data were pooled with those from our previous GWAS of AD and of a further 862 controls. The overall sample comprised 1,333 male in-patients with severe DSM-IV AD and 2,168 controls, all of German descent. Single marker tests were performed. In addition gene based tests, pathway analysis (global test) and a polygenic score based analysis were carried out to assess the combined contribution of multiple markers.
Results: ADH1C SNP rs1789891 obtained genome wide significant association (p=1.27e-8) with AD. Gene based tests yielded significant associations for a high LD region around ADH1C/ADH1B genes. Pathway based analysis obtained significant results for functional groups “Carbohydrate Metabolism” (genes ADH1C, ADH7, ADH4, PGM1, AKR1C2), “Cell Adhesion” (CDH13), “Energy Metabolism” (LHPP, ATP6V0A4, SUMF1) and “Replication and Repair” (XRCC5). The polygenic score based approach showed a significant result (p=9.7e-9).
Conclusions: This is the first GWAS of AD performed in a Caucasian population to report genome-wide significant findings from single marker as well as from polygenic score based analyses. The results suggest the existence of a continuum of genetic effects, and that many more susceptibility genes await identification. Pathway based analysis may help to identify these genes and underlying biological pathways by integrating information from multiple SNPs at once.

Dysfunction of glutamatergic projection neurons in the medial prefrontal cortex of rats with a history of alcohol dependence

Presenting Author: WH Sommer
M Meinhardt (1), AC Hansson(1), S Perreau-Lenz(1), K Drescher (2), M Heilig (3), R Spanagel(1), WH Sommer (1)

(1) Dept. of Psychopharmacology, Central Institute of Mental Health, Mannheim,Germany

(2) GPRD, Abbott,Ludwigshafen, Germany

(3) Laboratory of Clinical and TRanslational Science, National Institut on Alcohol Abuse and alcoholism/NIH, Bethesda, USA

Understanding the pathophysiology of addictive disorders is critical for development of new treatments. A prolonged history of alcohol dependence persistently up-regulates voluntary alcohol consumption and behavioral stress responses. Although it is well established that the phenotype of protracted abstinence (the post-dependent state) is mediated by hyperactivity of the amygdala, recent research demonstrates a critical role for the medial prefrontal cortex (mPFC) in the inhibition of addictive behaviours. The underlying neurobiology of altered mPFC function is poorly understood.
Microarray-based transcriptome analysis from mPFC, nucleus accumbens and amygdala tissue extracts from post-dependent rats followed by cluster analysis using cell-type specific gene sets (gene set enrichment analysis) pointed to mPFC projection neurons as a major site of long-lasting alcohol induced neuroadaptations. Using laser capture microscopy-aided microdissection followed by quantitative RT-PCR a subset of these genes (Egr2, Egr4, Nr4a1, Grm2) was found to be specifically downregulated in highly purified infralimbic projection neurons. Functionally, Grm2 (mGluR2) signaling seems strongly impaired in the corticostriatal circuitry of post-dependent rats as demonstrated by in vivo microdialysis.
Together, these data point towards profound alterations in mPFC function, in particular within the infralimbic region, and predict dysfunction of inhibitory control over behaviour in alcohol addiction. Treatments that target this region may help alleviate symptoms of addictive disorders.

MODULATING GENE-EXPRESSION OF ALZHEIMER'S DISEASE RELATED PROTEINASES ADAM10 AND BACE1

- A SCREENING APPROACH -

Presenting Author: Sven Reinhardt
Sven Reinhardt (1), Kristina Endres (1)

(1) University Medical Centre of the Johannes Gutenberg University, Mainz, Department of Psychiatry and Psychotherapy

Alzheimer's disease (AD) is a progressive, neurodegenerative disease implicating cognitive impairment and neuronal loss. A pivotal event during AD-pathogenesis is the proteolytic cleavage of the amyloid precursor protein (APP) by the β-secretase BACE1 (β-site APP cleaving enzyme1). This proteolysis leads to generation of neurotoxic A β-peptides, which are the key components of AD-characteristic amyloid plaques. Alternatively, APP can be cleaved by the a-secretase ADAM10 (a disintegrin and metalloproteinease10) within the A β-stretch. This prevents the release of A β-peptides; moreover cleavage generates neuroprotective sAPPa. Thus, increasing ADAM10 gene-expression represents a promising approach in AD therapy. Additionally, elucidating physiological contexts, in which a misbalance of gene expression of both proteinases emerges, might contribute to a deeper understanding of AD-pathogenesis.
For this approach, a dual cell-based luciferase reporter assay for the human promoters of either ADAM10 or BACE1 was established. 704 human transcription factors (TFs) and 640 compounds from a FDA approved drug library were screened for an influence on ADAM10 and/or BACE1 transcriptional activity in human neuroblastoma cells. The screening revealed 48 TFs and 46 compounds to significantly alter the ratio of ADAM10 to BACE1 promoter activity. To narrow the selection, TFs were classified according to their expression levels in the CNS of adults by using Expressed Sequence Tag (EST) profiles. The remaining 23 factors and the 46 substances were tested by reporter gene assays for modulating gene expression of the substrate APP. 15 of the selected transcription factors displayed common regulatory mechanisms regarding proteinase and substrate expression. 10 compounds revealed increased APP promoter activity and consequently were excluded from future analysis concerning the potential therapeutic value of substances.

Rapid-onset Dystonia-Parkinsonism: Exome sequencing in a German family reveals new candidate genes

Presenting Author: Katja Lohmann
Katja Lohmann (1), Katja Zschiedrich (1), Anne Weißbach (1), Susen Winkler (1), Kathrin Isbruch (2), Michael Schwarz (2), Christine Klein (1)

(1) University of Lubeck, Section of Clinical and Molecular Neurogenetics at the Department of Neurology

(2) Klinikum Dortmund, Department of Neurology

Background: Rapid-onset dystonia-parkinsonism (RDP) is a rare movement disorder characterized by a combination of dystonia and parkinsonism. It follows an autosomal dominant transmission pattern with reduced penetrance. In some families, RDP is caused by mutations in the ATP1A3 gene. However, in several patients mutation in this gene have been excluded suggesting at least one other RDP gene.
Methods: We investigated a four-generation German family with four living affected members. Mutations in ATP1A3 were previously excluded. We conducted a genome-wide linkage analysis. Next, exome sequencing was performed in two affected members. Novel variants that were localized in regions showing probable linkage and found in both individuals underwent several evaluation steps. First, we sequenced the respective variants in all four affected and in an additional 16 family members using Sanger sequencing to confirm the variant and to test for segregation. Second, frequencies of segregating variants were determined in German healthy control subjects.
Results: The genome-wide linkage analysis resulted in seven chromosomal regions with probable linkage. Exome sequencing revealed 183 undescribed variants (26 missense, 8 in untranslated regions, 35 silent, 114 intronic) in these regions common to both patients. Assuming that one of the missense variants causes pathogenicity, these variants underwent validation steps. Twelve of the 26 missense variants were excluded because they were not confirmed by Sanger sequencing (n=6) or did not occur in all affected family members (n=6). Another ten variants were excluded because they occurred homozygously in unaffected family members or had allele frequencies in controls >1%.
Conclusions: We have currently identified four novel missense variants as possible cause for RDP in a German family. Further analysis of unaffected controls and other patients with RDP will likely result in the identification of a novel RDP gene.

Interactome analysis and functional characterization reveals a role of Lrrk2 in actin cytoskeleton dynamics

Presenting Author: Andrea Meixner
Andrea Meixner (1,2), Karsten Boldt (1,2), Marleen Van Troys (3,4), Manor Askenazi (5,6,7,8), Christian J. Gloeckner (1,2), Matthias Bauer (1,9), Jarrod A. Marto (5,6,7), Christophe Ampe (3,4), Norbert Kinkl (1,2) and Marius Ueffing (1,2)

(1) Division of Experimental Ophthalmology, Institute for Ophthalmic Research, University of Tübingen, 72076 Tübingen, Germany, (2) Research Unit for Protein Science, Helmholtz Zentrum München - German Research Center for Environmental Health (GmbH), 85764 Neuherberg, Germany, (3) Department of Medical Protein Research, VIB, B-9000 Ghent, Belgium, (4) Department of Biochemistry, Faculty of Medicine and Health Sciences, Ghent University, B-9000 Ghent, Belgium, (5) Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston University, Boston, MA 02115, USA, (6) Department of Cancer Biology, Dana-Faber Cancer Institute, Boston, MA 02115, USA, (7) Blais Proteomics Center, Dana-Faber Cancer Institute, Boston, MA 02115, USA, (8) Department of Biological Chemistry, The Hebrew University of Jerusalem, 91120 Jerusalem, Israel, (9) Department of Neurology, Hertie Institute for Clinical Brain Research, University of Tübingen, 72076 Tübingen, Germany

Mutations in the leucine-rich repeat kinase 2 (Lrrk2) are collectively the most common cause of autosomal-dominant inherited and idiopathic Parkinson's disease (PD). The protein belongs to the ROCO protein superfamily and comprises various domains including a GTPase and kinase domain as well as several regulatory and protein-interaction domains. However, little is known about its involvement in the molecular pathogenesis of PD, primarily due to a limited understanding on the protein's physiological function. The wide distribution of point mutations throughout the sequence of Lrrk2 and the presence of domains likely facilitating protein interactions suggest that protein-protein interactions could be crucial for the biological function of Lrrk2.
To investigate the molecular interaction network of endogenous Lrrk2 under stoichiometric constraints we applied QUICK (quantitative immunoprecipitation combined with knockdown) in NIH3T3 cells. The identified interactome was validated in silico and revealed actin isoforms and actin-associated proteins, collectively suggesting that the function of Lrrk2 is related to actin-based cytoskeletal dynamics. In fact, we found de novo binding of affinity purified human Lrrk2 to F-actin in vitro and could demonstrate that Lrrk2 itself is able to modulate actin polymerization. On the cellular level, the lentiviral-mediated knockdown of Lrrk2 by small hairpin RNA (shRNA) expression led to morphological alterations in NIH3T3 cells. In developing dopaminergic midbrain primary neurons, the prime cellular target site of defects in PD, the loss of Lrrk2 expression resulted in reduced neurite outgrowth, a process critically dependent on proper actin cytoskeleton dynamics. Hence, our data suggest a physiological role of Lrrk2 in actin-related cellular processes, whose impairment may underlie PD-associated neuro-degeneration.

Mapping of LRRK2 phosphorylation sites – a protein kinase associated with Parkinson's disease

Presenting Author: Christian Johannes Gloeckner
Christian Johannes Gloeckner (1,2), Karsten Boldt (1,2), Felix von Zweydorf (1,2), Sandra Helm (1), Hakan Sarioglu (1), Marius Ueffing (1,2)

(1) Helmholtz Zentrum München, Research Unit Protein Science, Neuherberg, Munich

(2) University of Tuebingen, Institute for Ophthalmic Research, Medical Proteome Center, Tuebingen, Germany

Mutations in leucine-rich repeat kinase 2 (LRRK2) that increase its kinase activity associated with familial forms of Parkinson's disease (PD). As phosphorylation determines the functional state of most protein kinases, we systematically mapped LRRK2 phosphorylation sites. Titanium dioxide phosphopeptide enrichment and subsequent mass spectrometric analysis using multistage activation (MSA) resulted in a fine mapping of the phosphorylated residues within the peptide sequence. Our analysis revealed a high degree of constitutive phosphorylation in a narrow serine-rich region preceding the LRR-domain. Allowing de novo autophosphorylation of purified LRRK2 in an in vitro kinase assay prior to mass spectrometric analysis, we discovered multiple sites of autophosphorylation. The results obtained by this method characterize LRRK2 as a true serine-threonine kinase.
Autophosphorylation mainly targets the Roc GTPase domain and its clustering around the GTP binding pocket of Roc suggests cross-regulatory activity between kinase and Roc domain. In addition, in order to get mechanistic insights into autophosphorylation on a site-specific level, a quantitative approach has been established based on stable isotope labeling of amino acids in cell culture (SILAC). Preliminary results show that autophosphorylation of sites within the Roc domain occur in a cis-mode rather than in trans suggesting that the Roc-kinase domain interaction is an intramolecular rather than an intermolecular process.

Genome-wide genotype data in Parkinson's disease: Meta-analysis and homozygosity

Presenting Author: Claudia Schulte
Claudia Schulte (1), Thomas Gasser (1) and the International PD Genetics Consortium

(1) Department of Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research and German Center for Neurodegenerative diseases (DZNE), University of Tuebingen, Germany

The goal of this project is to systematically analyze genetic risk factors in Parkinson's disease (PD). These analyses are based on large patient and population cohorts ascertained at our center and as part of a consortium with international collaboration partners. Previously we have conducted a genome wide association study (GWAS) in PD and identified two significant risk factors, MAPT and SNCA, and evidence for LRRK2 and PARK16. To identify novel risk loci for PD, we did a meta-analysis of datasets from five PD GWAS from the USA and Europe (discovery phase). The discovery phase consisted of 5333 case and 12019 control samples, with genotyped and imputed data at 7 689 524 SNPs. The replication phase consisted of 7053 case and 9564 control samples. We identified 11 loci that surpassed the threshold for genome-wide significance ($p<5\times10–5$). Six were previously identified loci (MAPT, SNCA, HLA-DR, BST1, GAK and LRRK2) and five were newly identified loci (ACMSD, STK39, MCCC1/LAMP3, SYT11, and CCDC62/HIP1R). This study provides evidence that common genetic variation plays an important part in the cause of PD. Further analysis in our GWAS data showed an increased level of genomic homozygosity in PD patients as compared to healthy individuals. Large stretches of homozygous SNPs are a sign of shared ancestry and indicate that there are likely to be further autosomal recessive genes that have not yet been cloned by traditional methods. These data provide an insight into the genetics of PD and the molecular cause of the disease and could provide future targets for therapies.

Gain and Loss of Lrrk2 - Two Mouse Models of Parkinson's Disease

Presenting Author: Daniela Vogt Weisenhorn
Florian Giesert (1) Lisa Glasl (1), Giovanni Piccoli (2), Julia Zerle (1), Karina Kloos (1), Ulrich Hafen (1), Andreas Hofmann (1), Ralf Kühn (1), Marius Ueffing (2), Sabine Hölter-Koch (1), Daniela Vogt Weisenhorn (1), Wolfgang Wurst (1,3,4)

(1) Institute of Developmental Genetics, Helmholtz Zentrum München – German Research Center for Environmental Health, Munich, Germany

(2) Research Unit Protein Science, Helmholtz Zentrum München – German Research Center for Environmental Health, Munich, Germany

(3) Max Planck Institute of Psychiatry, Munich, Germany

(4) Technical University Munich, Germany

Mutations in the Leucine-rich repeat kinase 2 (Lrrk2) have been shown to be associated with late-onset autosomal dominant Parkinson´s Disease (PD). Pathogenic variations linked to PD can be found in the GTPase, the COR and the Kinase domain of this multidomain protein. In order to study pathogeneic mechanisms induced by specific mutations we generated a mouse model of PD by introducing the missense mutation R1441C into the endogenous murine Lrrk2 gene. Moreover, to study the physiological function of the protein, we generated a constitutive knockdown model.
No obvious age-related neurodegeneration neither in the dopaminergic nor in other neurotransmitter systems can be observed - both in Lrrk2 R1441C and in Lrrk2 knockdown animals. Also no signs of inclusion bodies or tau-pathology could be detected. Accordingly, no overt motor symptoms can be observed. Nevertheless, several alterations reminiscent of pre-motor symptoms observed in "early" PD patients and LRRK2 mutation carriers were observed in both mouse lines. They show nearly identical alterations in depression- and anxiety-related behaviour, reduced olfaction and subtle gait alterations. However, at the cellular level – at which we could provide hints for a role of the protein in cytoskeleton organisation as well as synaptic transmission – the R1441C mutation rather leads to opposing effects when compared to the loss-of-function effect. This might indicate that LRRK2 dysfunction and loss of LRRK2 alters distinct cellular processes in opposite directions, resulting, however, on the systemic level in similar dysfunctions. Interestingly, in the constitutive models the cellular phenotypes are reduced, hinting towards the presence of compensatory mechanisms. Taken together, both Lrrk2-mutant lines recapitulate early, non-motor symptoms are therefore valid mouse models of presymptomatic Parkinson's disease, in which compensatory mechanisms are still overruling the destructive effect of the mutations.

Wild-type alpha-synuclein leads to cell death in postmitotic human dopaminergic neurons.

Presenting Author: M. Höllerhage
Matthias Höllerhage (1), Anderson De Andrade (1), Joachim Goebel (1), Wolfgang H. Oertel (1), Bastian Hengerer (2), G. U. Höglinger (1)

(1) Dept. of Neurology, Experimental Neurology, Philipps-University Marburg, Marburg, Germany

(2) CNS Diseases Research, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

Parkinson's disease (PD) is characterized by the presence of intracellular protein inclusions called Lewy bodies. The main component of Lewy bodies is a small 140 aa long protein called alpha-synuclein. The physiological function of alpha-synuclein is not fully understood but it is supposed to play a role in synaptic plasticity. Rare mutations (A30P, A53T, E46K), duplications or triplications of the alpha-synuclein gene lead to early-onset, severe phenocopies of PD. These finding suggest that alpha-synuclein plays an important role in the pathophysiology of PD. Although interesting concepts have emerged, the mechanisms, by which alpha-synuclein induces degeneration of dopaminergic neurons are largely unknown. Despite the general belief that alpha-synuclein or some of its derivatives are neurotoxic, there are surprisingly only very limited reports about the successful development of experimental models, in which wild-type or mutant alpha-synuclein leads to neurotoxicity. Here we present for the first time a model in which overexpression of wild-type alpha-synuclein leads to cell death in human postmitotic dopaminergic neurons.

Lund human mesencephalic (LUHMES) cells are derived from 8 week old human embryonic midbrain neuronoblast, immortalized Tetracyclin-controlled overexpression of the oncogen v-myc. We verified that LUHMES neurons upon differentiation show all features of human postmitotic dopaminergic midbrain neurons (no BrdU incorporation, expression of dopaminergic markers (TH, AADC, VMAT2, DAT, GIRK2), no expression of non-dopaminergic or glial markers). With adenoviral vectors we achieved an overexpression of alpha-synuclein in wild-type or mutant forms (A30P, A53T) with a transduction rate of 83.7±0.8%. As control, we overexpressed GFP. In our model we see alpha-synuclein-mediated toxicity, as determined biochemically (LDH-release) and microscopically (nuclear condensation), with the mutant variants being significantly more toxic than the wild-type protein.

Impact of Calpain Cleavage of alpha-Synuclein in the Pathogenesis of Parkinson's Disease by Mouse-Models

Presenting Author: Meike Diepenbroek
Meike Diepenbroek (1), Silke Nuber (1), Thomas Ciossek (2), Jeanette Huebener (1), David Lynch (3), Ronald Melki (4), Laura, Pieri (4), Makoto Higuchi (5), Jiro Takano (5), Takaomi C. Saido (5), Philipp J. Kahle (6), Mala V. Rao (7), Ralph A. Nixon (7), Markus Zweckstetter (8), Olaf Riess (1)

(1) Dept.Medical Genetic, University of Tuebingen, Germany, (2) Nycomed GmbH., Present address: Boehringer Ingelheim Pharma, Germany, (3) Dept.Neurology, Pathology and Laboratory Medicine,The Children's Hospital of Philadelphia, USA, (4) Laboratoire d'Enzymologie et Biochimie Structurales, Centre National de la Recherche Scientifique, France, (5) Laboratory for Proteolytic Neuroscience, RIKEN Brain Science Institute, Wako, Saitama, Japan, (6)Laboratory of Functional Neurogenetics, Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University Clinics Tuebingen, Tuebingen, Germany, (7)Center for Dementia Research, Nathan S. Kline Institute, Orangeburg, New York 10962, Departments of Psychiatry, (8)Max-Planck-Institute for Biophysical Chemistry, Göttingen, Germany

Parkinson´s disease (PD) is a common neurodegenerative and slowly progressive disorder. Mutations and gene multiplications of the alpha-synuclein (aSyn) gene are known to cause familial PD.
a-synuclein is a small soluble protein and it is expressed primarily at presynaptic terminals throughout the brain. The precise function of aSyn is unknown so far but it has been identified as a major protein component of Lewy bodies (LBs) and Lewy Neurites (LNs), which are the neuropathologic hallmark of PD disease brain. Mechanisms by which aSyn switches conformational state, leading to an accumulation of presumambly toxic oligomers and insoluble aggregates are still unknown, but recent evidence point towards a toxic gain of function of C-terminal truncated aSyn fragments.
Calpain is a calcium-activated protease and it was shown that alpha-synuclein is a substrate for calpain cleavage. Further, calpain plays a role in the aggregation of C-terminal truncated aSyn and may contribute to toxicity of fibrillized alpha-synuclein by cleaving within the C-terminus.
Therefore, our study is focused on the functional implication of calpain-mediated proteolytic cleavage of aSyn in the pathogenesis of PD.
In order to analyze the neurotoxic impact of calpain-cleaved aSyn, we generate and characterize two contrasting mouse models, expressing human mutant [A30P] aSyn either in mice overexpressing human calpastatin or in mice on a calpastatin-deficient background. First analyses showed neuropathological alteration in the brain stem and nigra of 7 month old mice, including differences of protein redistribution, paralleled by an increase astrogliosis. Western Blot Analysis brought first evidence of alterations in content low-molecular fragments of aSyn in the brain stem of double-mutant mice. We will continue our research focussing on specifying fragments and its impact on neuropathology and functional deficite at different time points in our mice.

Similar induction of PARKIN, PINK1, PLA2G6 and other Parkinsonism genes during serum deprivation and starvation

Presenting Author: Suzana Gispert-Sanchez
Michael Klinkenberg (1), Marina Jendrach (1), Isabelle Braun (1), Filomena Ricciardi (1), Michael Walter (2), Blas Morales-Gordo (3), Georg Auburger (1), Suzana Gispert-Sanchez (1)

(1) Department of Neurology, Bldg 89, Goethe University Medical School, Theodor Stern Kai 7, D-60590 Frankfurt, Germany

(2) Department of Medical Genetics, Institute of Human Genetics, University of Tuebingen, Calwer Str. 7, D-72076 Tuebingen, Germany

(3) Movement Disorder Unit, Hospital Universitario San Cecilio, Avenida Doctor Olóriz 16 E-18012 Granada, Spain

Parkinson's disease (PD) is the most frequent neurodegenerative movement disorder and manifests at old age. While many details of its pathogenesis remain to be elucidated, in particular the protein and mitochondrial quality control during stress response have been implicated in monogenic PD variants.
Here, we sought to define to what extent trophic signals and starvation stress are relevant for the function of the ubiquitin ligase PARKIN, the mitochondrial kinase PINK1 and other PD genes. Initially, in a global transcriptome survey of primary human skin fibroblasts with PARKIN loss-of-function strong expression differences of growth factor signaling components were observed. Conversely, serum deprivation and nutrient starvation of human fibroblasts, primary mouse neurons and human SH-SY5Y neuroblastoma cells after 8 to 24 hours time course was found to induce PARKIN transcript levels up to 6-fold. The corresponding 3-fold starvation-induction of PARKIN protein was limited by its translocation and autophagic consumption in lysosomes during this process. Investigating whether other Parkinsonism genes show regulated expression after starvation, an early phasic upregulations was detected for PLA2G6, LRRK2 and ATXN3 transcripts, early constant upregulation for FBXO7 and SQSTM1, later phasic upregulation for ATXN2, then PARKIN, PINK1 and finally MAPT, in contrast to a downregulation for ATP13A2. After pharmacological suppression of trophic signals, PARKIN, PINK1, PLA2G6 and ATXN3 showed coregulation in unstarved cells. Ablation of autophagy resulted in similar expression regulation for PARKIN, PINK1 and PLA2G6. Proteasome inhibition failed to suppress the starvation-triggered inductions only for LRRK2, ATXN3 and SQSTM1.
In conclusion, this systematic expression survey suggests sequential protective roles of PLA2G6, PARKIN and PINK1 in autophagic starvation response.

Characterization of loss of Parkinson's disease-associated protein DJ-1 (PARK7) in human and rodent *ex vivo* models

Presenting Author: Guido Krebiehl
Guido Krebiehl (1,2,3,*), Carolin D. Obermaier (1,2,3,4,*), Benjamin Schmid (2,3,*), Lena F. Burbulla (1,2,3,4), Susanna A. Heck (2,3), Thomas Gasser (2,3) Rejko Krüger (1,2,3)

(1) Laboratory of Functional Neurogenomics

(2) DZNE, German Center for Neurodegenerative Diseases, Tübingen, Germany, (3) Department of Neurodegenerative Diseases and Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany,

(4) Graduate School of Cellular & Molecular Neuroscience, University of Tübingen, Tübingen, Germany

(*) authors contributed equally to this work

Loss of function mutations in the protein DJ-1 are a rare cause of neurodegeneration in familial PD. However, differential regulation of DJ-1 in the cerebrospinal fluid and saliva turned out to be a consistent biomarker for the common sporadic form of PD. In addition to its known functions, we recently showed that loss of DJ-1 function leads to impaired mitochondrial function with reduced lysosomal degradation of mitochondria in different cellular models.
Our studies now focus on the translation of our findings into a neuronal environment. We previously characterized the role of DJ-1 on mitochondrial function and dynamics as well as degradation of dysfunctional mitochondria in mouse embryonic fibroblasts and, more interestingly, in fibroblasts from patients with an inherited c.192G4C DJ-1 mutation. Western Blot analyses revealed that the homozygous c.192G4C mutation in the DJ-1 gene leads to an unexpected almost complete loss of the protein in fibroblasts from our index patient. The same effect was found on RNA-level by qPCR suggesting that the disease-associated mutation leads to instability of mRNA, hence resulting in loss of the protein. Live cell imaging studies further revealed already typical alterations of mitochondrial morphology in fibroblasts from a presymptomatic homozygous carrier. This indicates that the characteristic mitochondrial phenotype may be observed even before first PD-symptoms arise. Further, first experiments in primary neurons give evidence that loss of DJ-1 has negative influence on mitochondrial transport along axons and dendrites. The generation of iPS from c.192G4C DJ-1 fibroblasts and subsequent differentiation into dopaminergic neurons will offer the possibility to validate these findings in a celltype specific for PD.
Our studies provide insight into the consequences of loss of DJ-1 in different ex vivo models and reveal neuron-specific alterations caused by impaired mitochondrial dynamics leading to neurodegeneration in PD.

Systematic interaction mapping links novel proteins to neurodegenerative disease processes

Presenting Author: Jenny Russ
Jenny Russ1, Pablo Porras-Millan1, Jean-Fred Fontaine2, Martin Schaefer2, Sean-Patrick Riechers1, Angeli Möller1, Michael Boutros3, Erich E. Wanker1

1 Neuroproteomics, Max Delbrueck Center for Molecular Medicine, 13092 Berlin, Germany; 2 Computational Biology and Data Mining, Max Delbrueck Center for Molecular Medicine, 13092 Berlin, Germany; 3 Division of Signaling and Functional Genomics, German Cancer Research Center, 69120 Heidelberg, Germany

Neurodegenerative diseases are progressive brain disorders that have several pathological mechanisms in common. Detailed understanding of these mechanisms remains elusive. In recent years, protein-protein interaction (PPI) networks have become important resources to unravel the molecular basis of diseases. Here, for the first time, we have created a PPI network for 389 target proteins predicted to be involved in neurodegenerative disease processes, including well known disease proteins such as huntingtin (HTT), α-synuclein and TDP-43. The screened target proteins were selected from the human proteome based on a bioinformatics assisted scoring system. We identified 14,033 predominantly novel interactions through stringent automated yeast two-hybrid screening. To obtain a high confidence PPI network, ~1,000 protein interactions were validated in mammalian cells utilizing a LUMIER co-immunoprecipitation assay. Additionally we developed a bioinformatic PPI scoring system using functional annotation measures and domain-domain interactions. For a set of 1,200 target proteins we also generated disease-related knock-down data by studying their influence on HTT and TDP-43 aggregation. Network clustering analysis allowed us to predict protein complexes involved in disease relevant processes such as RNA processing and protein degradation. We verified the disease relevance of 12 complexes with knock-down experiments and identified 13 huntingtin and 22 TDP-43 aggregation and toxicity modifiers, most of which have not been described previously.

Modulation of Protein Complex Composition and Function involved in Neurodegenerative Diseases

Presenting Author: Tanja Kurtz
Tanja Kurtz (1), Melanie Heßler (1), Verena Lehmann (1), Irina Czogiel (1), Fabian Hosp (2), Matthias Selbach (2) and Bodo M. H. Lange (1)

(1) Max Planck Institute for Molecular Genetics, Berlin, Department of Vertebrate Genomics

(2) Max Delbrück Center for Molecular Medicine, Berlin-Buch, Intracellular Signalling and Mass Spectrometry

Many efforts have been made to increase our understanding of the cause, progression and mechanism leading to neurodegenerative disorders like Alzheimer's disease, Parkinson's disease or amyotrophic lateral sclerosis. Whereas most of these diseases are sporadic and of unknown cause, a series of different gene mutations have been identified to cause familial variants of several neurodegenerative disorders. It is the aim of this project to identify neurodegenerative disease relevant protein-protein interactions, and to characterise the identified protein complexes for modelling disease related signalling pathways on a biochemical and functional level.
To achieve this goal we have adapted an inducible Flp-In T-REx HEK 293 cell culture system to the GATEWAY high-throughput cloning system for transfection and efficient generation of stable cell lines. We produced 35 stable cell lines expressing a C- or N-terminal TAP-fusion protein for SOD1, SNCA, APP, ATXN1, PARK2, PARK7, PSEN1, HTT and TARDBP (wild type and mutant forms). Native protein complexes are isolated by tandem affinity purification (TAP) and analysed by mass spectrometry. Functional assays are further employed to study the morphological and cellular traits as a consequence of neuronal disease related protein overexpression of wild type and mutant variants. Performing of an image based screen with subsequently computational analysis will define the effect of neurodegenerative disease relevant proteins on cell morphology and cytoskeletal organisation. Disease-relevant cues such as cellular stress or co-expression of upstream regulatory kinases will be applied in our cellular system to investigate the consequence of such modulation on neurodegenerative protein complex composition and cellular function.

Suppression of Hyperpolarization-activated Cyclic nucleotide-gated Non-selective cation (HCN) channel Activity in Forebrain Neurons affects early Development and Adult Behavior in Mice

Presenting Author: Andrea Merseburg
Andrea Merseburg (1), Fabio Morellini (1) and Dirk Isbrandt (1)

(1) DFG Heisenberg Team Experimentelle Neuropädiatrie - Zentrum für Molekulare Neurobiologie Hamburg (ZMNH)

The development of the brain and its neuronal networks is a sequence of events during which neurons are born, migrate, arborize, and establish transient or persistent synaptic connections. Any pathological changes of ion channel expression and function during these complex processes can result in neurodevelopmental disorders that may persistently affect learning ability, memory, and behavior. The present study was aimed at investigating developmental contributions of hyperpolarization-activated cyclic nucleotide-gated nonselective cation (HCN) channel deficiency to structural, behavioral, cognitive, and physiological alterations of transgenic mice that conditionally express a dominant-negative HCN subunit (hHCN4-G480S) under the control of the calcium-calmodulin dependent kinase II (CaMKII) promoter. Suppression of HCN channel activity resulted in lower body weight, behavioral hyperactivity, alterations in novelty-seeking and anxiety levels, and changes in working memory and spatial learning and memory. Furthermore, telemetric electrocorticogram recordings in freely moving mice revealed increased cortical theta (4 10 Hz) oscillations in the active phase of waking and during paradoxical (REM) sleep, and increased delta power (0.5-4 Hz) during slow wave sleep of mutant mice compared to control littermates. Blockade of the Na^{+} K^{+} 2Cl cotransporter (NKCC1) during the neonatal period did not prevent the behavioral and network alterations observed in the mutant mice. In conclusion, transgenic suppression of HCN channel currents in the forebrain resulted in neurodevelopmental abnormalities that are associated with persistent behavioral hyperactivity and altered cortical network activity. Attenuation of GABA-mediated excitation by blockade of NKCC1 during the neonatal period did not prevent behavioral and network hyperactivity in mutants with suppressed activity of HCN channel-mediated Ih.

Whole Exome Sequencing in a large GEFS+ Family

Presenting Author: Julian Schubert
Julian Schubert(1), Yvonne Weber(1), Felicitas Becker(1), Peter Frommolt(2), Christian Becker(2), Holger Lerche(1)

(1) Hertie Institute for Clinical Brain Research, Tübingen

(2) Cologne Center for Genomics, Cologne

We evaluated a large GEFS+ family by using a whole exome sequencing approach for 3 family members.
In average we had 86 million reads and around 90 % of the reads were covered with at least 10-fold.
To narrow down the data we did an intersection of these 3 exomes and a stringent filtering. The out coming mutations were validated by Sanger Sequencing.
Four novel mutations which are not reported in dbSNP 131 and the 1000 Genomes Project data were filtered out. Three are nonsynonymous coding variants and one is leading to a stop codon. All four mutations are in different genes.
Additionally these mutations were checked in a control cohort of 188 individuals.
Cosegregation-analysis of these mutations, showed that there is no full match of pheno- and genotype.
The most promising mutation, which codes for a stop codon is recently under further investigation.
At the moment we are sequencing the gene carrying that mutation in additional individuals having the same phenotype. Furthermore functional studies of these mutations have been planned.

Promoter variants determine GABA-related transcription in human epileptic brain

Presenting Author: Katharina Pernhorst
Katharina Pernhorst (1), Anna Raabe (2), Pitt Niehusmann (1), Karen M.J. van Loo (1), Alexander Grote (3) , Per Hoffmann (4) , Sven Cichon (4), Thomas Sander (5) , Susanne Schoch (1), Albert J. Becker (1)

(1) Department of Neuropathology, University of Bonn Medical Center

(2) Department of Epileptology, University of Bonn Medical Center

(3) Department of Neurosurgery, University of Bonn Medical Center

(4) Department of Genetics, University of Bonn Medical Center

(5) Cologne Center for Genomics, University of Cologne

Functional consequences of single nucleotide polymorphisms (SNPs) associated with episodic brain disorders, i.e. epilepsy and depression, remain often unresolved. For rs1883415 (ALDH5A1; succinic semialdehyde dehydrogenase) and rs4906902 (GABRB3; GABAA beta3) present in the 5'-regulatory region of genes relevant for GABA-homeostasis, allelic associations with generalized epilepsies have been reported. We addressed their allelic association with episodic brain disorders and allele-specific impact on the transcriptional regulation of the respective genes in human brain tissue. From pharmacoresistant temporal lobe epilepsy (TLE; n=146) patients, DNA and mRNA were isolated from hippocampi cryopreserved after epilepsy surgery and used for allelic association and real time qRT-PCR analyses complemented by in vitro promoter studies. The C-allele of rs1883415 is accumulated in TLE compared to controls (n=651). The rs4906902 A-allele is overrepresented in patients with depression. Cis-acting regulatory effects are increased ALDH5A1 mRNA in individuals homozygous for the C-allele and reduced GABRB3 transcripts in individuals homozygous for the G-allele. Bioinformatic analyses suggest that rs1883415 and rs4906902 alter the DNA binding affinity of the transcription factors (TFs), Egr-3 in ALDH5A1 and MEF-2 in GABRB3 promoters, respectively. Using in vitro luciferase transfection assays, we observed that in both cases the TFs regulate gene expression in dependence of the allelic variant in the same direction as observed in the human hippocampi. Our data suggest a substantial relevance of genetic promoter variants for the expression of corresponding genes in brain tissue of patients suffering from episodic CNS disorders. In the future, genetic profiling of such variants may open the perspective to enable 'personalized' pharmacotherapies more effective for chronic recurrent brain disorders.
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Role of accessory subunits in determining antiepileptic drug resistance of sodium channels

Presenting Author: M. Uebachs
Mischa Uebachs (1), Toralf Opitz (1), Gesa Dickhof (1), Michel Royeck (1,2), Marie T.Horstmann (1,3,4), Lori L.Isom (5), H.Beck (1)

(1) Department of Epileptology

(2) Department of Neurosurgery, University Medical Center Bonn

(3) Helmholtz-Institute for Radiation and Nuclear Physics

(4) Interdisciplinary Center for complex Systems, University of Bonn

(5) Department of Pharmacology, University of Michigan

Neuronal excitability is critically determined by the properties of voltage-gated Na^+ currents. Fast transient Na^+ currents (INaT) mediate the fast upstroke of action potentials, whereas low voltage activated persistent Na^+ currents (INaP) contribute to subthreshold excitation. Na^+ channels are composed of a pore-forming alpha subunit and one or two beta subunits that are known to modify the biophysical properties of pore-forming subunits.
In this study we adress the idea that beta subunits might alter the pharmacological properties of Na^+ channels. We have examined the effect of the anticonvulsant carbamazepine (CBZ) on INaP in mice lacking either the beta1 (Scn1b) or beta2 (Scn2b) subunit and their wild-type littermates.
Surprisingly, we found that CBZ induced a significant shift of the voltage-dependence of activation of INaP to more hyperpolarized potentials. This novel CBZ effect on INaP was strongly enhanced in Scn1b null mice, leading to a pronounced increase of INaP at subthreshold potentials. Current-clamp recordings and computational modelling studies revealed that this effect causes a complete loss of CBZ efficacy in reducing repetitive firing.

Thus, beta subunits modify not only the biophysical but also the pharmacological properties of Na^+ channels with respect to INaP. These results suggest that altered expression of beta subunits in neurological disorders may cause altered neuronal sensitivity to drugs targeting Na^+ channels.

Functional Characterization of Novel GABA(A) Receptor Mutations Associated with Idiopathic Generalized Epilepsies

Presenting Author: Snezana Maljevic
Merle Bock (1), Julia Knaus (1), Julian Schubert (1), Timm Danker (2), Steven Petrou (3), Epicure Consortium, Yvonne Weber (1), Snezana Maljevic (1), Holger Lerche (1)

(1) Hertie Insitute for Clinical Brain Research, Dept. of Neurology and Epileptology, University of Tübingen, Germany

(2) NMI Natural and Medical Sciences Institute at the University of Tuebingen, Germany

(3) Florey Neuroscience Institutes, Australia

Several mutations affecting genes encoding alpha-1 or gamma-2 subunit of the GABA(A) receptor have been associated with idiopathic generalized epilepsies (IGE). Within the Epicure Consortium, 66 ion channel genes were screened in 95 index patients of families with IGE. Of the 78 detected variants, 9 were found in genes encoding different GABA(A) receptor subunits. To assess the pathogenecity of these variants and understand better the role of GABA(A) receptors in epileptogenesis, we set out to functionally analyze these variants. Using site-directed mutagenesis, detected mutations were introduced into the cDNAs encoding affected human GABA(A) receptor subunits and studied using Xenopus laevis oocyte expression system and automated two-electrode voltage-clamp recording technique. Two mutations affecting different genes encoding GABA(A) receptor subunits, the GABRB2 (encoding beta-2) and the GABRA5 (coding for alpha-5) were found completely cosegregating with the absence seizures within the same family. Functional analysis provided for both mutations revealed a reduced GABA-induced response as compared to the WT receptors. Additionally, another variant affecting the GABRA5 gene detected in a different family also presented with a clear loss-of-function. These data suggest that the GABRB2 and the GABRA5 present potential novel epilepsy genes. Hence all subunits of the most abundantly expressed GABA(A) pentamer composed of 2 alpha-1, 2 beta-2 and a gamma-2 subunit have now been associated with IGE. Furthermore, GABRA5 mutations might indicate a novel dysinhibition pathomechanism in epileptogenesis, since GABA(A) receptors containing alpha-5 subunits are primarily expressed in the hippocampus and localized to extrasynaptic regions of pyramidal neurons where they mediate the tonic inhibition. Further studies of detected GABA(A) receptor variants should enable us to define several highly probable new causative genes associated with epilepsy.

Nav1.1 knock-in mice as a model for GEFS+: Channel dysfunction leading to dysinhibition in different brain regions.

Presenting Author: Ulrike Hedrich (1)
Ulrike Hedrich (1), Melinda Martin (2), Camille Liautard (3), Massimo Mantegazza (3), Andrew Escayg (2), Holger Lerche (1)

(1) Dept. of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, Otfried-Mueller-Str. 27, D-72076 Tuebingen, Germany

(2) Department of Human Genetics, Emory University, 615 Michael Street, Whitehead Building, Suite 301, Atlanta, Georgia 30322

(3) IN2M-IPMC, Nice-Sophia Antipolis, 660 Route des Lucioles, 06560 Valbonne, France

Neuronal voltage-gated sodium channels (NaV) are essential for the generation and propagation of action potentials. It has previously been shown that mutations of the SCN1A gene, encoding the a-subunit of the NaV1.1 neuronal sodium channel, can lead to different neurological disorders, amongst others generalized epilepsy with febrile seizures plus (GEFS+). One of the first identified human GEFS+ mutations within the SCN1A gene is R1648H, which is located in the voltage sensor of domain IV. To study the effects of this mutation on the neuronal excitability, we used a knock-in mouse model carrying the human GEFS+ mutation NaV1.1-R1648H (Martin et al., JBC, 2010).
We performed whole-cell patch clamp recordings in acute brain slices to examine the firing properties of inhibitory and excitatory neurons in different brain regions. Inhibitory neurons within the cortical layer V, the hippocampal stratum oriens (CA1) and the thalamic reticular nucleus of heterozygous animals showed a decreased firing rate compared to their wild-type littermates. The membrane properties such as input resistance and resting membrane potential did not differ between heterozygous and wild-type inhibitory neurons. In contrast excitatory pyramidal cells of the cortical layer V, the hippocampal stratum pyramidale as well as the excitatory relay neurons of the thalamic ventrobasal area did not show any differences between heterozygous and wild-type animals. Additionally we could show that tonic as well as phasic inhibition is decreased in thalamus and cortex. Thus, our data suggest a decreased excitability of inhibitory neurons in different brain regions of the SCN1A-R1648H knock-in mice, which may lead to epileptic seizures and this could also be true for GEFS+ patients.

The psychiatric susceptibility gene CACNA1C and its sex-specific relationship with personality traits, depressive symptoms, and cognitive function in the general population

Presenting Author: Jana Strohmaier
Jana Strohmaier (1), Ludwig A. Hothorn (2), Stephanie H. Witt (1), Vanessa Nieratschker (1), Daniel Gerhard (2), Sandra Meier (1), Stefan Wüst (1), Adrian Loerbroks (3), Josef Frank (1), Til Stürmer (4,5,6), Manfred Amelang (7), Marcella Rietschel (1), Thomas G. Schulze (8)

(1) Central Institute of Mental Health, Division of Genetic Epidemiology in Psychiatry, Mannheim, Germany, (2) Institute of Biostatistics, University of Hannover, Germany, (3) Social and Preventive Medicine, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany, (4) Division of Pharmacoepidemiology and Pharmacoeconomics and Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, USA, (5) Department of Epidemiology, University of North Carolina, Gillings School of Global Public Health, Chapel Hill, North Carolina, (6) Department of Internal Medicine VI, University of Heidelberg, Germany (7) Institute of Psychology, University of Heidelberg, Germany, (8) Department of Psychiatry and Psychotherapy, University Medical Center, Georg-August-University, Goettingen, Germany

Introduction: Recent genome-wide association studies report strong evidence for an association between the A-allele of rs1006737 in CACNA1C and affective disorders and schizophrenia. We assessed the relationship of rs1006737 with endophenotypes of these disorders in a large longitudinal cohort study. We applied a specific analytical method designed to assess a possible sex-specific mode of inheritance and genotypic effect of rs1006737.
Methods: A population-based sample of 3793 subjects aged 40-65 was screened for personality with the Eysenck-Personality-Inventory, the State-Trait Anger Expression Inventory, the Sense of Coherence Scale, the Life Orientation Test, for perceived social support, depression, and psychoticism. All subjects were genotyped for rs1006737.
Results: In men, the A-allele of rs1006737 was associated with lower sense of coherence (p=0.010) and perceived social support (p=0.015) and more depressive symptoms at follow up (p=0.0067). The genotypic effect of the A-allele was additive for sense of coherence and depressive symptoms at follow-up, and recessive for perceived social support. In women, the AA-genotype was associated with higher sense of coherence (p=0.001) and perceived social support (p=0.035), and lower neuroticism (p=0.035) and psychoticism (p=0.045). The genotypic effects of the A-allele were recessive.
Conclusion: The risk variant rs1006737 is associated with personality and depressive symptoms, i. e. with psychological well-being, in the general population. The mode of inheritance and geneotypic effects are sex-specific. Our results emphasize the need for adequate sex-specific genetic analyses to detect important genotype-sex interaction effects. Further, our data suggest that phenotype characterization in psychiatric genetic association research needs to cover the whole continuum from maladaptive to adaptive/competent functioning.

BDNF and NTRK2 Polymorphisms and Antidepressant Treatment Response

Presenting Author: Johannes Hennings
Johannes M Hennings (1), Martin A Kohli (1,2), Darina Czamara (1), Christiane Wolf (1), Angela Hecka (3), Katharina Domschke (4), Volker Arolt (4), Bernhard T Baune (5), Sonja Horstmann (1), Tanja Brückl (1), Torsten Klengel (1), Andreas Menke (1), Bertram Müller-Myhsok (1), Marcus Ising (1), Manfred Uhr(1), Susanne Lucae(1)

(1) Max Planck Institute of Psychiatry, Munich, Germany

(2) John P. Hussman Institute for Human Genomics, Miami, USA

(3) University of Basel, Institute of Psychology, Basel, Switzerland

(4) Department of Psychiatry, University of Muenster, Muenster, Germany

(5) Department of Psychiatry, The University of Adelaide, Adelaide, Australia

Background: Data from clinical studies and results from animal models suggest a major involvement of the neurotrophin system in the pathology of depression and antidepressant treatment response. Genetic variations within the genes coding for the brain-derived neurotrophic factor (BDNF) and its key receptor Trkb (NTRK2) may therefore influence the response to antidepressant treatment.
Methods: We performed a pharmacogenetic study in 398 at least moderately severe depressed Caucasian inpatients participating in the Munich Antidepressant Response Signature (MARS) study. We tested for single marker association of 82 SNPs tagging the BDNF and NTRK2 gene regions with antidepressant treatment response. In an attempt for replicating the results, we genotyped all nominally significant associated SNPs of the discovery analysis in additional 249 patients of the MARS study and 247 depressed inpatients from an independent sample recruited in Münster, Germany.
Results: We identified several SNPs of the BDNF and NTRK2 gene that were significantly associated with antidepressant treatment response. We could partly replicate these associations in two additional depression samples and a combined analysis of all samples (total of 894 patients), withstanding correction for multiple testing.
Conclusions: These findings provide further substantiation for a possible involvement of genetic variations in the BDNF and NTRK2 gene in the antidepressant treatment response.

Validating P2RX7 as a susceptibility marker for depression using humanized mouse mutants

Presenting Author: Sandra M. Walser
Sandra M. Walser (1), Nina Dedic (1), Vladimira Jakubcakova (1), Mayumi Kimura (1), Mathias V. Schmidt (1), Wolfgang Wurst (2), Jan M. Deussing (1)

(1) Max Planck Institute of Psychiatry, Munich, Molecular Neurogenetics

(2) Helmholtzzentrum München, Neuherberg, Institute of Developmental Genetics

Recent linkage and association studies suggest P2RX7 as a novel susceptibility gene for major depressive disorder and bipolar disorder. A non-synonymous coding SNP (rs2230912, Gln460Arg) has been shown to be associated with reduced calcium influx and is likely to affect P2RX7 oligomerization and interaction. A meta-analysis including previous genetic studies supports a contribution of the P2RX7 polymorphism to increased susceptibility for the development of mood disorders. To study the functional relevance of the polymorphism in an appropriate in vivo model, we generated humanized mouse mutants in which the murine P2RX7 gene was substituted by the wild-type or the disease-associated isoform of human P2RX7 using a knock-in approach based on homologous recombination in embryonic stem (ES) cells. The correct expression of the human P2RX7 variants in the brain of mutant mice was confirmed by ISH using a human-specific probe. Moreover, we were able to demonstrate the different functional properties of wild-type and disease-associated human P2RX7 variants. The difference was evaluated by measuring their competence to mount an IL-1ß-response upon LPS/BzATP stimulation in peritoneal macrophages isolated from these mice. The polymorphism led to an increased IL-1ß secretion by macrophages isolated from mutant mice. Since stress in combination with a genetic predisposition can act as a trigger for processes that result in an increased risk of developing mood disorders, we subjected hP2RX7 mice to three weeks of chronic social defeat stress. Moreover, comprehensive analyses of sleep patterns have been performed. Mice with the heterozygous genotype showed an altered response to chronic stress and a reduced quality of sleep. Taken together, these humanized mouse lines are significantly contributing to functionally validate the human association data in vivo.

Response to Antidepressants is associated with Polymorphisms in the Leptin Gene and reduced Leptin availability

Presenting Author: Stefan Kloiber
Stefan Kloiber (1), Stephan Ripke (2), Benno Pütz (1), Johannes Hennings (1), Peter Weber (1), Marcus Ising (1), Manfred Uhr (1), Elisabeth Binder (1), Bertram Muller-Myhsok (1), Florian Holsboer (1), and Susanne Lucae (1)

(1) Max Planck Institute of Psychiatry, Kraepelinstrasse 2-10, Munich, Germany (2) Center for Human Genetic Research, MGH Simches Research Center Boston, MA, USA

Leptin, one of the key players in weight regulation, has been shown to exert antidepressant-like effects. Therefore we analyzed genetic variants in the leptin gene, leptin mRNA-expression, and leptin plasma concentrations in a sample of depressed inpatients from the Munich Antidepressant Response Signature (MARS) project. SNPs in the leptin gene were associated with response to antidepressant treatment. Results remained significant after correction for multiple testing and could be partially replicated in a second sample. Diminished leptin mRNA expression and decreased leptin levels could be linked to unfavorable treatment outcome. Our data thus point towards a role of leptin in antidepressant treatment response.

The non-synonymous P2RX7 SNP rs2230912 is associated with affective disorders:

Results from an association study in major depression and from a meta-analysis

Presenting Author: Susanne Lucae
Susanne Lucae, Darina Czamara, Manfred Uhr, Marcus Ising, Florian Holsboer, Bertram Müller-Myhsok

Max Planck Institute of Psychiatry, Munich, Germany

Since the first report of an association of SNPs in the P2RX7 gene with bipolar disorder (BD) eight subsequent studies have been published testing associations of the non-synonymous P2RX7 SNP rs2230912 with BD and/or major depressive disorder (MDD). While three studies reported association of this SNP, other studies did not detect significant associations. P2RX7 encodes a brain-expressed receptor, is involved in Ca^{2+} dependent signal pathways and may regulate immune function and neurotransmitter release. We tested rs2230912 for association with MDD in the Munich Antidepressant Response Signature (MARS) study (543 depressed patients versus 542 control subjects) and performed a meta-analysis taking into account the nine published studies as well as the additional tenth study.
In our association study with MDD a nominally significant association was observed for rs2230912 for the genotypic and the allelic (nominal $p = 0.025$) but not for the dominant or heterozygous-disadvantage model.
The meta-analysis however resulted in a significant effect of rs2230912 on MDD/BD case-control status in the heterozygous-disadvantage model ($p = 0.0028$). This effect is significant after correction for multiple testing.
Our association study and the meta-analysis thus further point towards a possible causal role of the non-synonymous P2RX7 SNP rs2230912 in affective disorders.

Association Fine-Mapping of the NCAN Gene, a Novel Risk Factor for Bipolar Disorder

Presenting Author: Thomas W. Mühleisen
Thomas W. Mühleisen (1,2), Anne Böhmer (1,2), Manuel Mattheisen (3,4), Tim Becker (5,4), Christian Meesters (5,4), Franziska A. Degenhardt (1,2), Lutz Priebe (1,2), Michael Alexander (1,2), Stefan Herms (1,2), René Breuer (6), Jana Strohmaier (6), Susanne Moebus (7), Markus Schwarz (8), Helmut Vedder (8), Jutta Kammerer-Ciernioch (8), Andreas Reif (9), Johanna Sasse (10), Michael Bauer (10), Martin Hautzinger (11), Xavier Miro (12), Andreas Zimmer (12), Johannes Schumacher (2), Thomas G. Schulze (13), Wolfgang Maier (14), Marcella Rietschel (6), Markus M. Nöthen (1,2), Sven Cichon (1,2,15)

(1) Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany, (2) Institute of Human Genetics, University of Bonn, Bonn, Germany, (3) Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, USA, (4) Institute of Medical Biometry, Informatics, and Epidemiology, University of Bonn, Bonn, Germany, (5) Genomic Mathematics in Neuroepidemiology, German Center for Neurodegenerative Diseases, Bonn, Germany, (6) Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Mannheim, Germany, (7) Institute of Medical Informatics, Biometry, and Epidemiology, University Duisburg-Essen, Essen, Germany, (8) Psychiatric Center Nordbaden, Wiesloch, Germany, (9) Department of Psychiatry, University of Würzburg, Würzburg, Germany, (10) Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Dresden, Germany, (11) Department of Clinical and Developmental Psychology, Institute of Psychology, University of Tübingen, Tübingen, Germany, (12) Institute of Molecular Psychiatry, University of Bonn, Bonn, Germany, (13) Department of Psychiatry and Psychotherapy, University of Göttingen, Göttingen, Germany, (14) Department of Psychiatry, University of Bonn, Bonn, Germany, (15) Institute of Neuroscience and Medicine (INM-1), Structural and Functional Organization of the Brain, Genomic Imaging, Research Center Juelich, Juelich, Germany

Bipolar disorder (BD) is a highly heritable and chronic disorder of mood, characterized by recurrent episodes of mania and depression. In a recent genome-wide association study (GWAS), we showed that common genetic variation (rs1064395) in the neurocan gene (NCAN) on chromosome 19p13.11 is a risk factor for BD (Cichon, Mühleisen et al., 2011).
To more characterize the association signal, we have now performed an association fine-mapping study. We aimed to perform high-density SNP genotyping in the associated region to identify the strongest associated (and thus potential pathophysiologically relevant) SNP(s), and to test for the presence of allelic heterogeneity. SNP selection was based on imputation of control genotypes using information from the 1000 Genomes Project and HapMap 3. After genotyping and quality control, 37 SNPs were analyzed in 1,139 patients with BD and 1,467 controls who represent an extension of the German sample of the original GWAS and follow-up. The mapped region of 465 kb comprised NCAN and seven genes downstream of rs1064395. Of 17 nominally significant markers across the locus ($p<0.05$), a SNP in an intron of NCAN showed a stronger association signal than rs1064395, the GWAS top SNP. Minor allele frequency difference between patients and controls was 7% for the new intronic SNP compared to 4% for rs1064395. Based on our current results, the new SNP is the most likely candidate for the functionally relevant SNP. Conditional single-marker analysis revealed that the new SNP explains the association signal at the locus completely. Haplotype analysis did not improve the result, suggesting that it is unlikely that a so far untested SNP is responsible for the association signal via linkage disequilibrium. To further strengthen its relevance in BD, we will test the new SNP in additional samples of BD. Eventually, functional studies are needed to shed light on the possible pathophysiological changes resulting from the presence of the risk allele.

Genome-wide supported risk variant for schizophrenia impacts on hippocampus activation during contextual fear conditioning

Presenting Author: Vanessa Nieratschker
Sebastian T. POHLACK (1), Vanessa NIERATSCHKER (2), Frauke NEES (1), Michaela RUTTORF (3), Stephanie H. WITT (2) , Marcella RIETSCHEL (2), Herta FLOR (1)

(1) Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Mannheim, Germany;

(2) Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Mannheim, Germany;

(3) Computer Assisted Clinical Medicine, Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany;

Key features of schizophrenia are declarative memory and contextual processing deficits. Recently, the neurogranin gene has been linked to schizophrenia in a genome-wide association study. Neurogranin is abundantly expressed in key regions of contextual learning and discrimination, such as the hippocampus. Further, abnormal functioning of the hippocampal formation as a major site for cognitive and contextual processing has been found in schizophrenia.
Contextual fear conditioning is heritable (35-45%) and constitutes a paradigm that is well suited to examine the impact of the genome-wide supported variant rs12807809 on cognitive and contextual processing. Hence, we employed an imaging genetics approach in healthy volunteers to investigate the influence of rs12807809 on the hippocampus during a contextual fear conditioning paradigm using structural as well as functional magnetic resonance imaging (fMRI). Carriers of the schizophrenia risk-allele variant showed significantly decreased activations in the left hippocampus during acquisition, indicating impaired hippocampal activity during contextual learning.
The present results suggest that contextual fear conditioning might constitute a valuable endophenotype for schizophrenia research. However, independent replication of our results is necessary.

Copy number variants in schizophrenia

Presenting Author: Dan Rujescu
Dan Rujescu

University of Munich, Dept. of Psychiatry

A major challenge in medicine is to understand genetic, molecular and cellular mechanisms underlying common mental disorders including schizophrenia, which involve complicated genetic and environmental determinants. Schizophrenia is a common mental disorder, affecting 0.5-1% of the population. The last few years have witnessed an explosion of interest in human genetics of complex diseases. The knowledge resulting from the availability of the complete sequence of the human genome, the systematic identification of single nucleotide polymorphisms (SNPs) throughout the genome, and the development of parallel genotyping technology (microarrays) established the conditions that brought about the current revolution in our ability to probe the genome for identifying disease genes. Genome-wide association (GWA) studies have opened a window into the biology of common complex diseases and have provided proof of principle. This is of utmost importance given that this knowledge can translate into the development of better treatment or even cure.

The talk will especially focus on new found common and rare genetic variants presenting the newest and most promising results from large genome-wide efforts including tens of thousand of patients and controls. Structural chromosomal abnormalities are emerging as an important genomic cause of neuropsychiatric diseases, including mental retardation, autism and more recently schizophrenia. A significant fraction of individuals with neurodevelopmental diseases including schizophrenia carry CNVs and many will be defined as “genomic disorders” in the coming years. The question is if a substantial number of schizophrenia cases are caused by rare copy number variations and if we going to define a number of new diseases at the interface between mental retardation, autism and schizophrenia. These new directions will be presented and critically discussed in this talk.

Key cellular genes play key role in X-linked disorders of cognition

Presenting Author: Vera Kalscheuer
Vera M. Kalscheuer (1), Hao Hu (1), Stefan A. Haas (1), Jamel Chelly (2), Hilde Van Esch (3), Martine Raynaud (4), Arjan de Brouwer (5), Tomasz Zemojtel (1), Stefanie Weinert (6), Guy Froyen (7), Suzanna G.M. Frints (8), Michael I. Love (2), Mark A. Corbett (9), Alison Gardner (10), Saffron Willis-Owen (10), Chuan Tan (10), Kathryn L. Friend (10), Ruping Sun (1), Anna Hackett (11), Mike Field (11), Eric Haan (9), John Nelson (12), Gill Turner (11), Gareth Baynam (12), Gabriele Gillessen-Kaesbach (13), Ulrich Müller (14), Daniela Steinberger (15), Bartlomiej Budny (16), Anna Latos-Bielenska (17), Lilian B. Ousager (18), German Rodriguez Criado (19), Marie-Louise Bondeson (20), Andreas Dufke (21), Monika Cohen (22), Lionel Van Maldergem (23), Tjitske Kleefstra (5), Marjolein Willemsen (5), Martin Vingron (1), Klaus Wrogemann (1), Reinhard Ullmann (1), Jozef Gecz (9), Andreas Tzschach (1), Hans van Bokhoven (5), Thomas J. Jentsch (6), Wei Chen (1,6), Hans-Hilger Ropers (1)

(1) Max Planck Institute for Molecular Genetics, Berlin, Germany, (2) University Paris Descartes, Paris, France, (3) Center for Human Genetics, University Hospitals Leuven, B-3000 Leuven, Belgium, (4) Inserm U930 "Imaging and Brain", Tours, France, (5) Department of Human Genetics, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, (6) Max-Delbrueck-Centrum fuer Molekulare Medizin, Berlin, Germany, (7) Human Genome Laboratory, Department for Molecular and Developmental Genetics, VIB, Leuven, Belgium, (8) Department of Clinical Genetics, Maastricht University Medical Center, azM, Maastricht, The Netherlands, (9) SA Pathology, Women's and Children's Hospital, Adelaide, South Australia, Australia, (10) School of Paediatrics and Reproductive Health, The University of Adelaide, Adelaide, South Australia, Australia, (11) The GOLD Service, Hunter Genetics, Waratah, New South Wales, Australia, (12) Genetic Services of Western Australia, King Edward Memorial Hospital, Perth 6000, Australia, (13) Institut für Humangenetik, Universität zu Lübeck, Lübeck, Germany, (14) Institut für Humangenetik, Justus-Liebig-Universität Giessen, Giessen, Germany, (15) bio.logis Center for Human Genetics, Frankfurt a. M., Germany, (16) Department of Endocrinology, Metabolism and Internal Diseases, Poznan, University of Medical Sciences, Poznan, Poland, (17) Chair and Department of Medical Genetics, Poznan University of Medical Sciences, Poznan, Poland, (18) Department of Clinical Genetics, Odense University Hospital, Odense, Denmark, (19) Unidad de Genética Clínica, Hospital Virgen del Rocío, Sevilla, España, (20) Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden, (21) Institut für Humangenetik, Abteilung Medizinische Genetik, Tübingen, Germany, (22) Kinderzentrum München, München, Germany, (23) Centre de Génétique Humaine, Université de Franche-Comté, Besançon, France

Vast genetic heterogeneity underlying the complexity of many common disorders, including intellectual disability has important implications for gene discovery. To advance our understanding of the molecular causes of intellectual disability, we have screened X-chromosome exomes in >250 probands from unrelated families using deep sequencing. Ninety one families were resolved and 8 novel genes with pathogenic mutations in multiple families, as well as 6 highly likely novel genes with truncating mutations in single families were identified. Protein truncating and read-through changes in 3.7% of the X-chromosome genes were considered as likely non-pathogenic. Several missense mutations and a truncating mutation were discovered in one of the novel genes, indicating a common role in ID. The new disease genes and previously identified others cluster into common molecular processes, such as transcription regulation, protein ubiquitination and networks of the postsynaptic density. This study serves as a model for the elucidation of monogenic and complex neurological disorders at the level of single genes and at the level of shared pathological mechanisms.

Duplication in chromosomal band 19q13.4 may be associated with syndromic mental retardation

Presenting Author: Albrecht Röpke
Albrecht Röpke, Cornelie Müller-Hofstede, Peter Wieacker, Axel Bohring

Institut für Humangenetik, Universität Münster, Münster, Germany

We report on a six years old girl with distinctive facial features, hypotonia, mental retardation with significant speech delay, and hyperactive, attention seeking behavior. Motor development was slightly delayed. MRI of the brain and EEG were reported to be normal. Metabolic screening, GTG-banded chromosomes (550 bands), FMR1 gene analysis, and methylation test at the SNRPN locus were normal.
Array CGH analysis uncovered a de novo interstitial duplication within chromosomal region 19q13.41-q13.42. This 264 kb duplication encompasses four genes NLRP12, MYADM, PRKCG, and CACNG7. Furthermore, this region includes the chr19q13.41 microRNA (miRNA) cluster (C19MC) of 48 miRNAs.
The distal breakpoint is located within the CACNG7 gene, which encodes a member of the Ca^{2+} channel gamma subunit family. Expression of the human CACNG7 has been localized specifically to brain. This gene is structurally similar to the mouse stargazin gene, where mutations have been associated with absence epilepsy.
The functional consequence of the miRNA cluster duplication is still unknown. Although it has been shown that miRNAs play an important role in neuronal development and differentiation, little is known about the mechanisms on how miRNAs might direct synapse initiation or maturation.
Several patients with a similar duplication in 19q13.4 have been collected. Further analyses of these cases are necessary to characterize the spectrum of clinical findings in these patients.

The Glut1 syndromes

Presenting Author: Yvonne G. Weber
Yvonne G. Weber and Holger Lerche

Abteilung Neurologie mit Schwerpunkt Epileptologie am Universitätsklinikum Tübingen und Hertie Institut für klinische Hirnforschung Tübingen

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 SLC2A1 coding for Glut1 have been found in the classical Glut1-deficiency syndrome (Glut1-DS), a severe syndrome of early childhood with drug resistant epilepsy, microcephaly and progressive mental retardation. Recently, we detected mutations in SLC2A1 in patients with paroxysmal exercise-induced dyskinesia (PED) and, in cooperation with others, also in patients with a special form of an idiopathic generalized epilepsy, the early onset absence epilepsy (EOAE) and patients with a permanent and slightly progressive paraparesis combined with PED (CSE). The symptoms respond well to a ketogenic diet providing ketone bodies instead of glucose to the brain as the main energy source. Thus, the clinical spectrum of the Glut1 syndromes was dramatically enlarged in the last three years. All detected mutations were functionally tested and reduced the uptake of glucose by the transporter significantly. The abstract summarizes the clinical, genetic and functional data of the Glut1 syndromes and gives hints to genotype-phenotype correlations.

An Unusual Neurological Syndrome of Crawling Gait, Dystonia, Pyramidal Signs, and Limited Speech and Deafness

Presenting Author: Beenish Arif
Beenish Arif (1), Anne Grunewald (2), Amara Fatima (1),Alfredo Ramirez (2), Arif Ali (3), Norbert Bruggemann (2), Jens Wurfel (4),Arndt Rolfs (5),Katja Lohmann (2), Akbar Malik (6),Christine Klein (2),and Sadaf Naz (1)

(1) School of Biological Sciences, University of the Punjab, Lahore,Pakistan;

(2) Section of Clinical and Molecular Neurogenetics,Department of Neurology, University of Lubeck, Lubeck, Germany;

(3) Services Hospital, Lahore, Pakistan;

(4) Institute of Neuroradiology, University of Lubeck, Lubeck, Germany;

(5) Albrecht-Kossel-Institutefor Neuroregeneration, University of Rostock, Rostock, Germany;

(6) The Children Hospital and Institute of Child Health, Lahore, Pakistan

Some movement disorders are characterized by distinct gaits that may or may not be part of rare syndromes. Many gene mutations including mitochondrial gene mutations might be involved in neurological disorders. The purpose of this study was to identify and molecularly characterize a neurological syndrome in a consanguineous Pakistani family. Five individuals of the family presented with an early-onset unusual neurological syndrome including generalized dystonia and variable degree of spasticity with lower-limb hyperreflexia and pyramidal signs. Bipedal locomotion was absent in 3 of the 5 affected individuals, whereas 2 patients walk bipedally with a severely dystonic-spasticgait. Other clinical features include cognitive impairment, limited speech, and deafness. Genotypes of all affected and unaffected siblings were obtained by Affymetrix SNP arrays, and revealed 6 linked regions under an autosomal dominant model of inheritance with reduced penetrance: 1q42.3–q43, 3p26.3–p26.1, 9p21.1–q21.3, 16q21–q23.1, 20q13.2–q13.33, and 21q22.3. An 8cM-region was identified on chromosome 9p21.1–p11.2 at which the affected individuals were heterozygous for the same parental allele combinations, consistent with a recessive mode of inheritance with compound heterozygous mutations in the same gene. The 2 unaffected siblings carried different allele combinations. These intervals did not contain any known dystonia gene. Sequencing of the most promising candidate genes was performed but no mutation was detected. The mitochondrial genome was sequenced using DNA from blood, hair follicles and urine samples, but no mutation was identified. Whole genome sequencing will be the next step to look for one or more gene mutations responsible for this complex syndrome.

The D620N mutation in the VPS35 gene in a German patient with early-onset Parkinson disease

Presenting Author: Kishore Raj Kumar
Kishore R Kumar, FRACP (1,2), Anne Weißbach, MD (1), Vladimir S Kostic, MD (3), Alfredo Ramirez, PhD (1,4), David K. Simon, MD, PhD (5), Johann Hagenah, MD (2), Christine Klein, MD (1), Katja Lohmann, PhD (1)

(1) Department of Neurogenetics and Neurology, University of Lübeck

(2) Department of Neurogenetics, Kolling Medical Institute, University of Sydney

(3) Institute of Neurology CCS, School of Medicine, University of Belgrade, Belgrade, Serbia

(4) Institute of Human Genetics, University Hospital Bonn, Bonn, Germany

(5) Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

To date, mutations in six genes (SNCA, LRRK2, Parkin, DJ-1, PINK1 and ATP13A2) have been well-validated as monogenic forms of hereditary Parkinson's disease (PD). Recently, two independent studies have implicated the D620N mutation in the gene Vacuolar Protein Sorting 35 (VPS35) as a cause of autosomal dominant PD in a Swiss and an Austrian family using exome sequencing. We performed screening for the D620N mutation in a large multi-ethnic population. One mutation carrier was identified, and this patient had a comprehensive clinical assessment. We describe the clinical findings and discuss the implications of these new developments.

Mitochondrial impairment in Parkinson’s disease patients with mutations in ATP13A2

Presenting Author: Anne Grünewald
Anne Grünewald (1), Björn Arns (1), Aleksandar Rakovic (1), Philip Seibler (1), Carolyn M. Sue (2), Christine Klein (1)

(1) University of Lübeck, Lübeck, Section of Clinical and Molecular Neurogenetics at the Department of Neurology

(2) Royal North Shore Hospital and University of Sydney, Sydney, Kolling Institute of Medical Research, Department of Neurogenetics

Background: Mutations in ATP13A2 are the cause of Kufor-Rakeb syndrome (KRS), a form of autosomal recessive Parkinson’s disease (PD) with dementia. The function and substrate specificity of the ATP13A2 protein are currently unknown. However, a link between ATP13A2 and lysosomal function has been described. Interestingly, several PD-associated proteins have recently been connected to a single pathway which regulates the autophagy of dysfunctional mitochondria. An involvement of ATP13A2 in this elimination process and, therefore, an influence of the protein on characteristics of the mitochondrial pool seems conceivable. This study investigates whether mutations in ATP13A2 impact on mitochondrial function and morphology in human fibroblasts.
Methods: Fibroblasts were obtained from three KRS cases with two mutant ATP13A2 alleles (c.1550C>T/c.1550C>T, c.3176T>G/c.3253delC and c.3057delC/IVS13+5:G>A) and four unrelated mutation-negative controls. Basal ATP levels and synthesis rates were determined luminometrically. The mitochondrial membrane potential was detected with JC-1. Oxygen consumption rates and extracellular acidification rates were measured on a Seahorse extracellular flux analyzer. The mtDNA integrity, mtDNA levels and PGC1-alpha mRNA expression levels were quantified by real-time PCR. The mitochondrial network was investigated immunocytochemically and interconnectivity was determined with image processing methods.
Results: In KRS patients, decreased ATP synthesis rates, increased mtDNA levels and more mtDNA lesions were detected. Assessment of the mitochondrial network morphology showed more fragmentation in ATP13A2 mutants than in controls.
Conclusions: Our findings indicate an involvement of ATP13A2 in bioenergetic mechanisms and mitochondrial dynamics, likely via the regulation of mitophagy.

Poster Presentation Abstracts

Symposium II

Genomics of Cardiac Disease and Metabolism

Next-Generation Sequencing Entering the Clinical Arena

Presenting Author: Jan Haas
J.Haas (1), A. Keller (2), W. Rottbauer (3), T.M. Strom (4), H.A. Katus (1), B.Meder (1)

(1) Department of Internal Medicine III, University of Heidelberg, Heidelberg, Germany

(2) Department of Human Genetics, Medical School, Saarland University, Homburg, Germany

(3) Department of Internal Medicine II, University of Ulm, Ulm, Germany

(4) Institute of Human Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

Over the last decade the genetic etiology of many heritable diseases could be resolved. For cardiomyopathies, mutations in more than 40 different genes have been identified. Due to this large genetic heterogeneity and missing of adequate gene-diagnostic tools, most patients are not genetically characterized, which would be paramount for individualized patient care.
Over the last years, next-generation sequencing (NGS) methods have developed rapidly, allowing now the analysis of billions of bases of sequence information in one single run. However, next-generation sequencing unselectively analyses whole genomic DNA, resulting in millions of reads that do not cover the regions of interest for the respective disease. Within the NGFN Transfer Innovation Alliance “Subgenome Fractionation” we develop tools and protocols for target enrichment and clinical NGS using array- and in-solution-based methods.
The efficient enrichment of subgenomic loci results in high sequence coverage of disease loci using only modest sequencing capacity, resulting in affordable costs for NGS-based genetic testing. Identification and interpretation of sequence variants is efficiently performed by a stepped bioinformatics pipeline, enabling us to discover known as well as novel variants. Using SIFT and in silico homology modeling, we select promising candidate mutations which possibly cause or modify the disease. Candidates are then further studied by co-segregation analysis, cohort studies and in vivo functional genomic approaches.

Molecular Characterisation of Uremic Toxins *in silico*

Presenting Author: Christopher Hardt
Christopher Hardt (1), Felix Dreher (1), Mona Köhler (2), Axel Kretschmer (3), Joachim Jankowski (2), Ralf Herwig (1)

(1) Max Planck Institute for Molecular Genetics

(2) Charité, Medizinische Klinik IV

(3) Bayer Healthcare AG

In uremia the kidney has restricted functions resulting in an abnormally high concentration of certain pathophysiologically active mediators in the blood. These retention solutes can cause severe organ damage, atherosclerosis and vascular remodeling. Recent reviews have identified at least 115 uremic retention solutes that were detected in increased concentrations in patients with renal failure across multiple studies. Although it has been pointed out that the retention of these toxins might constitute potent risk factors, summarized in the term uremic syndrome, a detailed molecular characterization is still missing. Besides, it remains clear that many more substances, that have not been detected yet, might exert toxic functions. In order to address these points we have performed a comprehensive in silico analysis. To expand the body of potential uremic toxins, we applied network analysis and over-representation analysis with respect to known pathways, gene ontology and other annotation in order to identify common interaction partners of the known uremic toxins and associated functional modules. Furthermore, we used statistical classification with respect to physico-chemical properties in order to find discriminating features between uremic retention solutes and other substances taken from the PubChem database. We used these methods to predict new potential markers for the uremic syndrome. We employed literature mining in order to assess co-association of these molecules with relevant terms.
In summary, this work presents the first in silico study of the uremic syndrome which allows us to prioritize known uremic toxins on the molecular level as well as to predict new potential toxins and is, thus, a complement to ongoing and future experimental studies.

10 Years of NGFN: Genome Wide Association Studies in Cardiac Arrhythmias: Recent Discoveries and Implications for Clinical Practice

Presenting Author: Stefan Kääb
Stefan Kääb (1), Moritz F. Sinner (1), Arne Pfeufer (2), Siegfried Perz (3), Martina Müller (1, 4), Annette Peters (4), Hugo A. Katus (5), H.-Erich Wichmann (4), Christian Gieger (4), Thomas Meitinger (6)

(1) University Hospital Munich, Campus Grosshadern, Medical Department I, Ludwig-Maximilians University Munich, Munich, Germany; (2) Institute of Genetic Medicine, EURAC research, Bolzano, Italy (3) Institute of Biological and Medical Imaging, Helmholtz Zentrum München, Neuherberg, Germany; (4)Institutes of Epidemiology 1 and 2, Helmholtz Zentrum München, Neuherberg, Germany; (5) Universität Heidelberg, Innere Medizin III / Kardiologie, Heidelberg, Germany (6) Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany

Genetic contribution to common cardiac arrhythmias has become an important aspect of current research and patient care. In the last 10 years, genome wide association studies (GWAS) have been used to identify the genetic underpinnings of all major quantitative traits from electrocardiographic parameters such as heart rate, PR-, QRS-, and QT-interval as surrogates for major myocardial electrical properties representing atrial, and ventricular conductance and ventricular repolarization respectively. In addition GWAS have identified a number of genetic loci associated with common cardiac arrhythmias, namely atrial fibrillation (AF) and sudden cardiac death (SCD).
GWAS have identified novel biological signals involved in human electrophysiology and disease. Findings from GWAS present tremendous opportunities to understand the mechanisms by which these novel pathways relate to human health and disease. Genetic variation only represents one aspect of a complementary network of signals that influence phenotypic variation. Epigenetic phenomena such as DNA methylation and gene silencing, as well as complex interactions between distinct genetic elements, differentially expressed transcripts, and metabolic and proteomic signals, may also explain a substantial proportion of phenotypic diversity. Bioinformatic techniques, improved phenotyping informed by molecular, electrophysiological, or refined clinical features may enhance the discovery of loci and networks that govern disease pathogenesis. Future research will focus on whether consideration of variants identified in GWAS can facilitate the identification of individuals at risk for disease, guide clinical management decisions, and relate to prognosis all measures essential for improved personalized medicine and care.

TRAF7 controls cardiomyocyte proliferation in zebrafish

Presenting Author: Eva Patzel
Eva Patzel, Steffen Just, Wolfgang Rottbauer

Department of medicine II, Universityhospital of Ulm, Ulm, Germany

Genetic programs which control cardiomyocyte proliferation remain largely unknown. The zebrafish has become a powerful model organism to identify new disease causing genes and the associated signaling pathways in cardiomyocyte proliferation.
We recently isolated the zebrafish mutant herzbuckel (hzb) in a large-scale ENU-mutagenesis screen for recessive lethal mutations that perturb cardiac function. hzb mutant embryos display severely reduced contractility of both heart chambers due to a significantly decreased cardiomyocyte amount. By a positional cloning approach we demonstrate that the herzbuckel phenotype is caused by a nonsense-mutation in the zebrafish TNF receptor-associated factor 7 gene (ztraf7), encoding for a novel E3-ubiquitin-ligase. Gene specific knock-down studies reveal a phenocopy of the hzb mutant phenotype whereas injection of wild-type traf7 mRNA in hzb mutant embryos rescues the mutant phenotype indicating that the hzb mutation is indeed responsible for the reduction of cardiomyocytes in hzb mutant embryos.
Since TRAF7-NFkB signaling is known to play a role in the regulation of cell proliferation in vitro we screened for differences in the proliferation behaviour in hzb cardiomyocytes. Interestingly, we find that the reduction in hzb cardiomyocyte quantity is indeed caused by a decreased proliferation rate. Additionally, we show that NFkB activity is downregulated in hzb mutants, suggesting that reduced NFkB activity might be the actual molecular cause of hzb phenotype.
These findings demonstrate for the first time an essential role of TRAF7-NFkB signaling in the regulation of cardiomyocyte proliferation in vivo.

MED10 regulates the formation of the atrioventricular canal by controlling Tbx2b expression in the embryonic zebrafish heart.

Presenting Author: Ina M. Berger
Ina M. Berger, Steffen Just, Wolfgang Rottbauer

Department of Medicine II, University Hospital Ulm, Ulm, Germany

The genetic and molecular mechanisms that guide valvulogenesis are mostly unknown but of immense importance for biomedical research since heart valve diseases account for up to 30% of all congenital cardiovascular malformations.
The zebrafish cardiac valve mutant ping pong (png) displays a pathologically developed atrioventricular canal accompanied by absent endocardial cushions, the precursors of the cardiac valves, and the vigorous regurgitation of blood between the atrial and ventricular chamber. By positional cloning, we identified an insertional promoter mutation within the zebrafish mediator complex subunit 10 (med10) gene leading to severely diminished med10 transcription and thereby to deficient endocardial cushion development. Injection of med10 mRNA in png mutant embryos restores the wild-type phenotype in these embryos. Interestingly, we find complete loss of tbx2b expression in the AV canal of png mutant hearts and demonstrate that transient reconstitution of Tbx2b expression rescues AV canal development in png mutant zebrafish. By contrast, overexpression of Foxn4, a known upstream regulator of Tbx2b, is not capable to reconstitute Tbx2b expression and thereby the formation of endocardial cushions in Med10-deficient png mutant hearts, suggesting a crucial role of Med10 in mediating Foxn4 signals and activating tbx2b transcription.
Thus, we provide for the first time evidence that heart valve development depends on the proper function of Med10 by regulating Foxn4-Tbx2b signaling in the developing AV canal.

Differential regulation of MicroRNA-582 in a murine knock-out model of DCM and an in vitro model of biomechanical stress

Presenting Author: Inka Boomgaarden
Inka Boomgaarden, Christian Kuhn, Derk Frank, Norbert Frey

University Medical Center Schleswig-Holstein, Kiel, Department of Cardiology

The homozygous loss of muscle LIM protein (MLP) in a transgenic mouse model results in dilated cardiomyopathy. Furthermore, mutations of the MLP-encoding CSRP3 gene have been shown to be associated with hypertrophic and dilated cardiomyopathy (DCM). We have identified a differentially expressed microRNA, mmu-mir-582, in hearts of MLP knock-out and wild type mice. The aim of this study was to further clarify the potential role of this microRNA in the pathogenesis of cardiomyopathies.
A bioinformatics screen of potential target mRNAs for mmu-miR-582 resulted in a number of genes which were screened for functional binding motifs with a dual luciferase reporter system (pmirGLO, Promega). Either mature microRNA showed differential abilities to suppress luciferase activity when using a perfect match positive control vector. From eight tested mmu-miR-582-5p targets, Art1 and Rcan3, and four tested mmu-miR-582-3p targets Pcdh19 3'-UTR binding sites showed strongest effects, respectively (up to -20% luciferase activity, $p<0,09$). To further assess the role of mir-582, its expression levels were also measured in an in vitro model of cardiac hypertrophy, namely neonatal rat ventricular cardiomyocytes subjected to cyclic stretch for 24 hours, resulting in 1,5-fold reduced expression of miR-582-5p.
In conclusion, we have identified murine mir-582 as differentially regulated in a murine knockout model of DCM, implicating a possible role of this microRNA in the etiology of cardiomyopathies. Furthermore, mechanical stretch lowered mmu-miR-582 expression while exhibiting hypertrophy-specific expression of the fetal gene program. Collectively, these data imply a potential role in the stretch sensing cellular machinery, as has already been proposed for MLP. The genomic location of mmu-miR-582 within the Pde4d gene locus and its co-regulated expression open up additional routes of investigation into mechanisms underlying possible combined effects.

Metabolomics in heart failure as a novel diagnostic tool

Presenting Author: Johanna Wolf
Johanna Wolf (1), Regina Reszka (4), Tanja Weis (1), Oliver Müller (1), Volker Liebenberg (4), Inken Padberg (3), Oliver Schmitz (3), Patricia Ruiz Noppinger (4) Norbert Frey (2), Jens Fuhrmann (3)*, Hugo A. Katus (1)*

*** joint senior authorship**

(1) Universitätsklinikum Heidelberg, Abteilung Innere Med. 3 (Kardiologie, Pulmologie, Angiologie)

(2) Universität Schleswig-Holstein, Campus Kiel, Klinik für Kardiologie und Angiologie

(3) metanomics GmbH, Berlin

(4) Metanomics Health GmbH, Berlin

Chronic heart failure has become the most prevalent cardiovascular disorder in the aging population of western countries. However early, specific and reliable biomarkers are missing to predict clinical progress and outcome.
On the molecular level, complex changes in protein composition and dysregulation of protein networks as well as altered energy metabolism lead to a functional deterioration of the myocardium. We therefore characterized the metabolome of blood, urine and myocardial samples in order to explore the diagnostic potential of metabolic markers or signatures in heart failure. Furthermore, our approach should yield novel insights into disease mechanisms and affected molecular pathways. Two complementary scientific strategies were followed. First, in carefully phenotyped patients with heart failure and healthy controls, metabolic profiles were obtained and related to the clinical phenotype and progression. Secondly, well defined animal models of heart failure were investigated.
Metabolite profiling was performed by untargeted as well as targeted GC-MS and LC-MS/MS based technologies, including dedicated methods for the detection of catecholamines, steroids, eicosanoids and a comprehensive lipidomics platform. In plasma and urine samples from patients, a clear metabolic signature of heart failure was identified already at early stages of the disease. Distinct subtypes of heart failure showed overlapping, but non-identical metabolic profiles. Compared to healthy controls, numerous pathways including lipid and amino acid metabolism were altered in patients. Neurohumoral activation could be followed both at the level of catecholamines as well as their catabolites. Importantly, the observed metabolic signature of heart failure was detected already at rest and largely preserved upon exercise testing.
Taken together, we demonstrate the diagnostic potential of a metabolomics approach based on plasma and urine in heart failure.

Myoscape (Muscle specific Calcium-Channel associated protein) is a novel striated muscle enriched gene modulating L-Type-Ca Channel Function

Presenting Author: Matthias Eden (3)
Matthias Eden (3); Benjamin Meder (1), Rainer Will (1), Mirco Völkers (1), Patrick Most (1), Wolfgang Rottbauer (2); Dieter Weichenhahn (1); Hugo A. Katus (1), Norbert Frey (3)

(1) Dept. of Internal Medicine III, University of Heidelberg, Heidelberg, Germany,

(2) Dept. of Internal Medicine II, University Hospital Ulm, Ulm, Germany

(3) Dept. of Cardiology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany

In around one third of all cases dilated cardiomyopathy (DCM) has a hereditary background. In an effort to identify novel candidate genes for human cardiomyopathy, we found a 105kd protein we named Myoscape, which is highly conserved between the species of human, mouse, rat and zebrafish. Myoscape expression is enriched in heart and skeletal muscle as determined by QPCR, northern and western- blot analysis. Immunolocalization of Myoscape showed a distinct co-localization with Alpha-actinin at sarcomeric Z-band. Next we identified Alpha Actinin and the C-terminal region of the L-Type Ca-channel as Myoscape interaction partners. Adenoviral knockdown of Myoscape in vitro using a specific GFP-tagged Micro-RNA in adult rat ventricular cardiomyoctyes (ARVCM) lead to significant decrease in global calcium transients. Analysis of L-Type Calcium currents by patch clamp technique in ARVCM revealed a significant impairment in L-Type channel function upon Myoscape ablation. Conversely, adenoviral overexpression of Myoscape significantly increases global Calcium transients and directly enhances L-Type Calcium channel currents. Moreover, overexpression of Myoscape restores decreased L-Type Calcium channel currents in failing ARVCM. As a functional consequence, adenoviral knockdown of Myoscape significantly reduces fractional shortening of ARVCM. In vivo antisense-morpholino based knockdown of Myoscape in zebrafish leads to severe cardiomyopathy. Screening a cohort of 244 Patients with dilated cardiomyopathy revealed several sporadic gene mutations in the human Myoscape gene locus which were all absent in a healthy control cohort of 280 Patients.
In summary, we identified a novel heart and muscle enriched protein we termed Myoscape which modulates L-Type Ca Channel function and force generation in vitro and in vivo and that might serve as a novel candidate gene for human cardiomyopathy.

The calcification relevant locus on chromosome 7, trans-activates osteogenic-related transcription factors Runx2 and Vdr to regulate the osteopontin expression.

Presenting Author: Zouhair Aherrahrou
Ann-Kathrin. Sowa (1), Frank J. Kaiser (2), Juliana Eckhold (2), Lars Doehring (1), Heribert Schunkert (1), Jeanette Erdmann (1), Zouhair Aherrahrou (1)

(1) Universität zu Lübeck, Lübeck, Medizinische Klinik II

(2) Universität zu Lübeck, Lübeck, Institut für Humangenetik

Cardiovascular calcification is prevalent in coronary artery diseases enhancing morbidity and mortality in Western countries. The transcription of osteopontin (Opn), an osteogenic marker, was found to be dramatically higher in mice predisposed for calcification. The role of the upstream transcription factors (TFs) regulating Opn remained unclear.

A panel of twelve osteogenic-related TFs that might regulate Opn were selected and analyzed for gene expression in heart dissections in C3H/He (C3H) mice predisposed to calcification and compared to resistant C57BL/6 (C57) mice using qPCR. Calcification was induced using freeze-thaw injury.
Among the tested TFs, a significant increase in gene expression was observed for Runx2, Sox9, Vdr and Nfκb in calcifying C3H mice compared to resistant mice. To test whether the transcription of Opn is directly regulated by these TFs we functionally analyzed the Opn promoter activity from C3H and C57 mice in luciferase reporter gene assays in cells co-transfected with each of the TFs. Whereas no changes in the activation of the Opn promoter was observed after co-transfection with Sox9 and Nfκb, Runx2 and Vdr were found to co-activate the Opn promoter activity of both mice strains. Interestingly, this effect was even more dramatic using the promoter constructs of the C3H mice predisposed to calcification as compared to resistant strains. Promoter sequence analysis between C3H and C57 mice revealed an insertion of TTTTTTTTTTTTA at the Runx2 binding site which seems to stabilize binding of Runx2. Interestingly, increase in the gene expression of Runx2 and Opn was also observed in the calcification-predisposed congenic mice, retaining the locus on chromosome 7 controlling calcification but share the same genetic background of Runx2, Vdr and Opn on chromosome 17, 15 and 5, respectively.
Thus our findings suggest that the locus on chromosome 7 trans-activates the activity of Runx2 and Vdr to activate downstream expression of Opn.

Whole exome sequencing in an extended family with myocardial infarction revealed a mutation in the gene adenylyl cyclase 8 (ADCY8)

Presenting Author: Anja Medack
Anja Medack (1), Janja Nahrstaedt (1,2), Klaus Stark (3), Sebastian Eck (4), Björn Mayer (1), Christian Hengstenberg (3), Inke R. König (2), Tim Strom (4), Thomas Meitinger (4), Heribert Schunkert (1), Jeanette Erdmann (1)

(1) Universität zu Lübeck, Medizinische Klinik II, Lübeck, Germany

(2) Universität zu Lübeck, Institut für Medizinische Biometrie und Statistik, Lübeck, Germany

(3) Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, Germany

(4) Helmholtz Zentrum München, Deutsches Forschungszentrum für Umwelt und Gesundheit, Institut für Humangenetik, Neuherberg, Germany

Background: Our group established a large collection of myocardial infarction (MI)-families with several affected first- and second-degree relatives. Based on two genome-wide linkage analyses with microsatellites and single nucleotide polymorphisms (SNPs) we found a linkage peak in one of the families on chromosome 8q24 spanning approximately 12 Mb. Our aim is to identify the underlying mutation for MI in this family by sequencing.
Methods: Whole exome sequencing in two affected cousins in this family was performed using the Agilent SureSelect 38 Mb Kit in the Helmholtz Zentrum in Munich.
Results and Discussion: We identified 26 potential deleterious mutations (missense and nonsense mutations) and in the whole exome evident in both family members. In the region on chromosome 8q24 only one potential disease-causing mutation was found. This valine to isoleucine exchange (p.V602I) in the gene adenylyl cyclase 8 (ADCY8) cosegregates with the disease in the family. p.V602I could not be found in 2,722 cases and 3,036 controls. ADCY8 encodes adenylate cyclase, a membrane bound enzyme that catalyses the formation of cyclic AMP from ATP in a calcium dependent fashion. The role in atherosclerosis remains elusive.
Conclusion: A combination of whole exome sequencing and linkage-analysis identified a mutation in ADCY8 leading to MI, however the functionality of this gene with regard to the disease remains unclear. Further experiments to establish the role of ADCY8 in CAD/MI are ongoing.

9p21 CAD risk haplotype shows altered up-regulation of IL12B and IL1B in macrophages after inflammatory stimuli

Presenting Author: Christa Zollbrecht
Christa Zollbrecht (1), Martina Grassl(1), Sabine Fenk (1), Regina Höcherl (1), Wibke Reinhard (1), Thomas Langmann (2), Klaus Stark(1)*, Christian Hengstenberg(1)*

(1) Klinik und Poliklinik für Innere Medizin II, Universitätsklinikum Regensburg, Germany

(2) Institut für Humangenetik, Universitätsklinikum Regensburg, Germany

Genome-wide association studies identified a risk haplotype on chromosome 9p21 to be associated with coronary artery disease (CAD). Since this region does not contain a clear candidate gene with known pathophysiology, we performed an allele-specific expression study in human macrophages during proinflammatory stimulation to investigate the function of this risk locus in the development of atherosclerosis and CAD.
Blood samples were taken from 40 stable male CAD patients either homozygous for risk (n = 20) or protective haplotype (n = 20) as well as from 28 healthy individuals (n = 14 for each haplotype). Monocytes were isolated and differentiated into macrophages via M-CSF. Besides control macrophages, cells were incubated with a proinflammatory IFNγLPS cocktail. After 24 h RNA was isolated and applied to Affymetrix Human Exon 1.0 ST Arrays.
In macrophages without stimulation only marginal expression differences could be detected between CAD patients with protective or risk haplotype. No significant changes were observed in healthy individuals and the combined data analysis. Addition of IFNγ/LPS up-regulated several interleukins, chemokine ligands and known inflammatory markers. We focused on differences in gene regulation due to the stimulus. As one of the most prominent genes IL12B showed higher up-regulation on basis of the 9p21 risk haplotype compared to the protective haplotype in all 3 datasets (CAD 33 %, healthy 37 %, combined 37 %). IL1B was less up-regulated in the risk group in all datasets (29 %, 13 % and 23 %, respectively).
We found different up-regulation of two interleukins in macrophages based on the different 9p21 haplotypes. We suppose that inducing inflammation in these cells is a good model for the in vivo situation and may help to reveal the impact of the 9p21 locus on development of atherosclerosis. These findings support the concept that IFNγ influences gene expression depending on 9p21 haplotype.

A novel rare non-synonymous mutation in the SH2B1 gene in overweight and obese individuals

Presenting Author: Anna-Lena Volckmar
Anna-Lena Volckmar (1), Ivonne Jarick (2), Nadja Knoll (1), André Scherag (3), Thomas Reinehr (4), Thomas Illig (5), Harald Grallert (5), H.-Erich Wichmann (5), Heike Biebermann (6), Heiko Krude (6), Pamela Fischer-Posovszky (7), Winfried Rief (2), Florian Bolze (8), Martin Klingenspor (8), Martin Wabitsch (7), Johannes Hebebrand (1), Anke Hinney (1)

(1) Department of Child and Adolescent Psychiatry, University of Duisburg-Essen, Germany, (2) Institute of Medical Biometry and Epidemiology, University of Marburg, Germany, (3) Institute of Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Germany, (4) Vestic Clinic of Children and Adolescent Medicine, Datteln, Germany, (5) Institute of Epidemiology, Helmholtz-Zentrum Munich, Germany, (6) Institute of Experimental Pediatric Endocrinology, Charité Berlin, Germany, (7) Department of Children and Adolescent Medicine, University of Ulm, Germany, (8) Research Center for Nutrition and Food Science, Technical University Munich, Germany

Introduction: Large-scale genome-wide association studies (GWASs) have identified 32 loci associated with body mass index in population-based samples of adults (Speliotes et al., Nat genet 2010).
Methods: We analysed these SNPs (or proxies) in our family-based (705 trios) and independent case-control (453 cases and 435 normal weight controls) GWASs for extreme early onset obesity. One of the best (according to p-value, directionally consistent) SNPs is rs2008514 (proxy of rs7359397, nominal ptrios=0.0094; pcc=0.052) in the vicinity of SH2B1 (Src-homology 2B adaptor protein 1 gene). Individuals with large deletions at chromosome 16p11.2 covering SH2B1 are obese (Bochukova et al., Nature 2010). We performed a mutation screen (dHPLC) in 95 extremely obese children and adolescents most likely harbouring mutations in the SH2B1 coding sequence. 90 individuals were selected based on over-transmission of the rs2008514 risk allele, while another 5 individuals were heterozygous for the deletion. Detected variants were genotyped (TaqMan, RFLP and ARMS-PCR) in independent large study groups (up to 3,839 obese and 10,838 controls).
Results: We identified three new rare mutations and four known SNPs (rs7498665, rs60604881, rs62037368, rs62037368) in SH2B1. Mutation A causes a non-synonymous, non-conservative exchange in the beta (ßThr/Ile) and gamma (γPro/Ser) splice variants of SH2B1. In silico analyses predicted a reduced function of ßSH2B1 for this mutation. It was only detected in three of 3,839 (extremely) obese or overweight children and adolescents, but not in 10,838 population based controls (p=0.034). A non-synonymous mutation B (Thr/Asp) and a mutation C at the 3’ end were only found in the screen, but not in the follow-up. For one of the SNPs (rs7498665) we observed evidence for transmission-disequilibrium (nominal p=0.019, OR= 1.19).
Conclusion: The rare variant ßThr/Ile/γPro/Ser of SH2B1 is associated with overweight/obesity. Functional implications need to be analyzed.

Missing Heritability in the Tails of Quantitative Traits? A Simulation Study on the Impact of Slightly Altered True Genetic Models

Presenting Author: Carolin Pütter
Carolin Pütter (1), Sonali Pechlivanis (1), Markus M. Nöthen (2,3), Karl-Heinz Jöckel (1), Heinz-Erich Wichmann (4,5), André Scherag (1)

(1) Institute for Medical Informatics, Biometry and Epidemiology, University Duisburg-Essen, Essen, Germany

(2) Institute of Human Genetics, University of Bonn, Bonn, Germany

(3) Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany

(4) Helmholtz Center Munich, German Research Center for Environmental Health, Institute of Epidemiology, Neuherberg, Germany

(5) Ludwig-Maximilians University Munich, Institute of Medical Data Management, Biometrics and Epidemiology, Chair of Epidemiology, Munich, Germany

Objective: Genome wide association studies (GWAS) have identified robust associations between single nucleotide polymorphisms (SNP) and complex traits. As the proportion of phenotypic variance explained is still limited for most of the traits, larger and larger meta-analyses are being conducted to detect additional associations. Here we investigate the impact of the study design and the underlying assumption about the true genetic effect in a bimodal mixture situation on the power to detect associations. Methods: We performed simulations of quantitative phenotypes analysed by standard linear regression and dichotomized case-control data sets from the extremes of the quantitative trait analysed by standard logistic regression. Results: Using linear regression, markers with an effect in the extremes of the traits were almost undetectable whereas analysing extremes by case-control design had superior power even for a much smaller sample sizes. Two real data examples are provided to support our theoretical findings and to explore our mixture and parameter assumption. Conclusions: Our findings support the idea to re-analyse the available meta-analysis data sets to detect new loci in the extremes. Moreover, our investigation offers an explanation for discrepant findings when analysing quantitative traits in the general population and in the extremes.

A microdeletion within a QTL hotspot on distal mouse chromosome 1 disrupts the Nob3 gene and modulates metabolic and neuronal phenotypes

Presenting Author: Heike Vogel
Heike Vogel (1), Stephan Scherneck (1), Timo Kanzleiter (1), Verena Benz (1), Reinhart Kluge (1), Matthias Blüher (2), Dirk Montag (3), Hans-Georg Joost (1), Annette Schürmann (1)

(1) Departments of Experimental Diabetology and Pharmacology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany

(2) Department of Medicine, University of Leipzig, Leipzig, Germany

(3) Research Group Neurogenetics, Leibniz-Institute for Neurobiology, Magdeburg, German

The New Zealand Obese (NZO) mouse develops a polygenic disease pattern of obesity, insulin resistance, and dyslipoproteinemia resembling the human metabolic syndrome. By positional cloning we have recently discovered two genes (Tbc1d1, Zfp69) to participate in the development of the disease. In an outcross population of NZO and the lean C57BL/6 (B6) mouse we identified a major obesity QTL on distal Chr.1. Introgression of a 38 Mbp segment of the QTL from NZO into the B6 background (B6.NZO-Nob3.38) increased body weight, running wheel and rotarod performance, and decreased anxiety. The Nob3.38 segment corresponds with a QTL hotspot (Qrr1) and is associated with diverse traits including behavioural phenotypes. Since 27 of 32 QTL were identified in crosses of different strains with B6, we hypothesized that B6 mice carry a pivotal alteration that is responsible for the complex Qrr1-mediated effects. We generated additional congenic lines, tested them for the trait body weight and defined a genomic interval comprising 43 genes. Expression analysis of genes located in the critical fragment revealed the most striking difference for one gene (Nob3 gene), encoding for a transcriptional regulator. In tissues of homozygous B6-animals the Nob3 gene was undetectable but expressed in NZO-allele carriers and in seven other strains. In contrast, expression of a cluster of 10 related genes was significantly higher in B6 than in NZO-allele carriers. Consistent with a regulation of the cluster by the Nob3 gene, overexpression of its mRNA in skeletal muscle of B6 mice suppressed the expression of other genes within the cluster. Sequence analysis identified a microdeletion including the first exon and the 5`-flanking region of the Nob3 gene in B6. We conclude that this microdeletion causes the knockout of the Nob3 gene, alters the expression of other family members, and is responsible for the complex behavioural and obesity-suppressing phenotypes conferred by Qrr1 of the B6 strain.

Metabolic Phenotyping of the Obese Mouse Mutant Line Mc4rW16X

Presenting Author: Nadine Rink
Nadine Rink (1), Florian Bolze (1), Ralf Kühn (2), Wolfgang Wurst (2), Martin Klingenspor (1)

(1) Technische Universität München, Molecular Nutritional Medicine, Else Kröner-Fresenius Center and ZIEL-Research Center for Nutrition and Food Science, Gregor-Mendel-Straße 2, D-85350 Freising, Germany

(2) Institute of Developmental Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Ingolstädter Landstraße 1, D-85764 Neuherberg/München, Germany

Loss-of-function mutations in the Melanocortin-4-receptor (MC4R) are responsible for obesity in about 6% of early onset-obese patients. Here we aim in vivo to characterize the stop mutation MC4RW16X which was identified in obese subjects. Therefore we generated a knockin mouse line carrying the Mc4rW16X allele by homologous recombination.
Metabolic phenotyping of Mc4rW16X knockin mice revealed elevated body weight due to an increase in fat mass compared to wildtypes starting at the age of 6 weeks. We determined energy balance by measuring energy intake and energy expenditure and conclude that hyperphagia and not hypometabolism causes obesity in Mc4rW16X knockin mice. Moreover we observed a trend towards a lower respiratory exchange ratio indicating a higher fatty acid oxidation in Mc4rW16X knockin mice. These results confirm that the novel knockin mouse line Mc4rW16X is a suitable animal model to study the physiological causes for the development of monogenic obesity and evaluate treatments.

Short-chain 3-L-hydroxyacyl-CoA dehydrogenase (SCHAD) and its role in the regulation of body weight and thermogenesis

Presenting Author: Nadja Schulz
Nadja Schulz (1), Heinz Himmelbauer (2), Michaela Rath (1), Sander Houten (3), Karsten Suhre (4), Stephan Scherneck (1), Heike Vogel (1), Reinhart Kluge (1), Petra Wiedmer (1), Hans-Georg Joost (1), Annette Schürmann (1)

(1) German Institute of Human Nutrition Potsdam-Rehbruecke, Germany, Department of Experimental Diabetology and Pharmacology

(2) Max Planck Institute for Molecular Genetics, Germany

(3) Academic Medical Center Laboratory Genetic Metabolic Diseases, The Netherlands

(4) Institute of Bioinformatics and Systems Biology, Germany, Helmholtz Zentrum München

Background: Dysregulation of fatty acid oxidation plays a pivotal role in the pathophysiology of obesity and insulin resistance. Medium- and short-chain 3-L-hydroxyacyl-CoA dehydrogenase (SCHAD; gene name: hadh) catalyzes the third reaction of the mitochondrial ß-Oxidation cascade, the oxidation of 3-hydroxyacyl-CoA to 3-ketoacyl-CoA, for medium and short-chain fatty acids. We identified hadh as a putative obesity gene by comparison of two genome wide scans, a quantitative trait locus (QTL) analysis performed in the polygenic obese NZO mouse and a siRNA-mediated mutagenesis in C. elegans.
Methods: For the physiological characterization of SCHAD, we deleted the gene with a gene trap approach and characterized the corresponding mouse model in respect to body weight, body composition, and thermoregulation under high-fat-diet conditions.
Results: Knockout mice were protected from diet-induced obesity, they exhibited lower body weight and fat mass than control mice. They did not differ in food intake, locomotor activity or energy expenditure. A lower respiratory quotient and excretion of acylcarnitines via the urine indicated that impaired fuel efficiency is responsible for the reduced body weight of hadh-/- mice. In addition, hadh-/- mice used more energy for thermogenesis, because they exhibited significantly higher body temperature than their wild-type littermates. In contrast, under acute cold exposure, hadh-/- mice did not maintain their body temperature because they were unable to use fat as an energy source under these conditions.
Conclusion: Our data indicate that an interruption of fatty acid oxidation at a late stage might be an approach for adiposity treatment.

KEGGtranslator: visualizing and converting the KEGG PATHWAY database to various formats.

Presenting Author: Florian Mittag
Clemens Wrzodek, Andreas Dräger, Andreas Zell

Center for Bioinformatics Tuebingen (ZBIT), University of Tuebingen, 72076 Tübingen, Germany.

The KEGG PATHWAY database provides a widely used service for metabolic and nonmetabolic pathways. It contains manually drawn pathway maps with information about the genes, reactions and relations contained therein. To store these pathways, KEGG uses KGML, a proprietary XML-format. Parsers and translators are needed to process the pathway maps for usage in other applications and algorithms. We have developed KEGGtranslator, an easy-to-use stand-alone application that can visualize and convert KGML formatted XML-files into multiple output formats. Unlike other translators, KEGGtranslator supports a plethora of output formats, is able to augment the information in translated documents (e.g. MIRIAM annotations) beyond the scope of the KGML document, and amends missing components to fragmentary reactions within the pathway to allow simulations on those.

A comparison of machine learning algorithms for disease risk prediction on Genome-wide association study (GWAS) data

Presenting Author: Florian Mittag
Florian Mittag, Michael Römer, Finja Büchel, Andreas Jahn, Andreas Zell

Center for Bioinformatics Tuebingen (ZBIT), University of Tuebingen, 72076 Tübingen, Germany.

In recent years, Genome-wide Association Studies (GWAS) helped identifying causal variants and risk factors of many complex diseases. Current, state-of-the-art genotyping platforms are able to measure hundreds of thousand to millons of single nucleotide polymorphisms (SNPs) at once, leading to a steadily increasing amount of data being generated. The statistical approaches in these studies usually rely on the independant evaluation of each SNP. This makes it hard to detect variants with only small effect size and usually requires a large number of samples.
Recent studies aimed at predicting the disease risk based only on genotype information by including all SNPs reaching certain predefined genome-wide thresholds. To this end, modern machine learning techniques, e.g., support vector machines, have been applied to create disease risk models in an unbiased manner. Different machine learning algorithms diverge not only in technical properties like computation time or complexity of the underlying model, but also in their ability to include SNP-SNP interactions or non-linear effects in their models.
In our study, we systematically investigated the performance of various machine learning algorithms when used to build disease-specific models and predict the phenotype of unseen samples. We included various algorithms of different complexity and type, such as the k-nearest neighbor algorithm, decision trees and random forests, artificial neural networks, and support vector machines. We applied these algorithms on case-control GWAS data sets (kindly provided by the Wellcome Trust Case-Control Consortium (WTCCC)) for multiple diseases, such as inflammatory bowel disease, coronary artery disease, bipolar disorder, hypertension, rheumatoid arthritis, and type 1 and type 2 diabetes, and present the different properties shown by those algorithms.

Genome-wide association study identifies four genetic loci associated with thyroid function.

Presenting Author: Rajesh Rawal
R. Rawal (1), C. Meisinger (2), A. Teumer (3), G. Homuth (3), H. Wallaschofski (4), T. Iittermann (5), B. O. Åsvold (6), T. Bjøro (7), K. H. Greiser (8,9) D. Tiller (9) A. Kluttig (9), H. Meyer zu Schwabediss (9), A. Doering (2,10) C. Gieger (1), H. Völzke (5)

1) Institute for Genetic Epidemiology, Helmholtz Zentrum München/Neuherberg, Germany, 2) Institute of Epidemiology II, Helmholtz Zentrum München/Neuherberg, Germany, 3)Interfaculty Institute for Genetics and Functional Genomics, Ernst-Moritz-Arndt-University Greifswald, Germany, 4) Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Germany, 5) Institute for Community Medicine, University Medicine Greifswald, Germany, 6) Department of Public Health, Norwegian University of Science and Technology, and Department of Endocrinology, Trondheim University Hospital, Trondheim, Norway, 7) Department of Medical Biochemistry, Oslo University Hospital, and Faculty of Medicine, University of Oslo, Oslo, Norway, 8) German Cancer Research Center (DKFZ), Division of Cancer Epidemiology, Heidelberg, Germany, 9) Institute of Medical Epidemiology, Biostatistics, and Informatics, Martin-Luther-University Halle-Wittenberg, 06097 Halle (Saale), Germany, 9) Department of General Pharmacology, University Medicine Greifswald, Germany; 10) Institute of Epidemiology I, Helmholtz Zentrum München/Neuherberg, Germany

Thyroid hormones play a key role in cellular growth, development and metabolism. Circulating concentrations of triiodothyronine (T3) and thyroxine (T4) are tightly regulated by thyrotropin (TSH) and have a strong heritable component. A large portion of heritability is supposed to be under polygenic control, but the genes responsible are mostly unknown.To identify genetic loci associated with thyroid function, we performed a discovery meta-analysis of genome-wide association studies including 4907 individuals (1287 individuals from the Cooperative Health Research in the Augsburg Region study and 3620 participants of the Study of Health in Pomerania. Four genetic loci were associated with serum TSH, three of them on a genome-wide and one locus on a borderline significance level. The first locus rs2046045 was located in the phosphodiesterase 8B (PDE8B) gene on chromosome 5q13.3. A second locus, rs10917469 was found upstream of and within the CAPZB gene (capping protein (actin filament) muscle Z-line,beta) on chromosome 1p36. A third locus associated with TSH, rs10028213, was located upstream of the nuclear receptor subfamily 3, group C, member 2 (NR3C2) gene on chromosome 4q31. Another locus, rs3813582, represents a “gene desert” on chromosome 16q23, located directly downstream of the predicted coding sequence LOC440389. All four SNPs were replicated in another sample from Norway (The Nord-Trøndelag Health (HUNT) study) and in one more population-based sample from Germany (Cardiovascular Disease, Living and Ageing (CARLA) study). In the combined analysis included 6,570 subjects the P value was 1.91 x 10-21 for rs2046045, 2.21 x 10-09 for rs10028213, 3.17x10-09 for rs3813582, and 2.69x10-08 for rs10917477 respectively. These four quantitative trait loci together accounted for 5 % of the variance in TSH serum concentration. These results may increase the knowledge about genetic factors and physiological mechanisms of thyroid function.

MODELING STEATOSIS AND STEATOHEPATITIS USING HUMAN INDUCED PLURIPOTENT STEM CELLS

Presenting Author: Justyna Jozefczuk
Justyna Jozefczuk (1), Martina Loibner (2), Kurt Zatloukal (2), Hans Lehrach (1), James Adjaye (1)

(1) Max Planck Institute for Molecular Genetics, Department of Vertebrate Genomics, Berlin, Germany

(2) Medical University of Graz, Institute of Pathology, Austria

Non-alcoholic fatty liver disease comprises a broad spectrum of disease states ranging from simple steatosis (S) to steatohepatitis (SH). In contrast to S which has a good prognosis and can be cured relatively easily, SH is associated with alterations of a variety of cellular functions including increased cellular stress that lead to serious hepatocyte injury and may result in liver cirrhosis and development of a lethal cancer - hepatocellular carcinoma. The major unsolved question is what genetic background and molecular mechanisms result in the development of SH followed by cirrhosis and cancer as compared to other individuals who develop only steatosis.
So far one of the biggest obstacles impeding studying the susceptibility to SH and its progression to hepatocellular carcinoma is the lack of a simplified in vitro system which would allow reproducible testing of the influence of various genetic and environmental factors on the etiology of this lethal disease.
The generation of patient-specific iPS cells followed by their differentiation into hepatocytes enables the analysis of steatosis and steatohepatitis in a reproducible, standarized and high throughput manner.
The main goals of our study is the generation of a system level dataset to enable the studying of the molecular mechanisms underlying the etiology of both diseases followed by the development of a computational model quantitatively explaining the response of S and SH hepatocytes towards various stimuli mimicking key aspects of environmental exposures potentially increasing the risk of developing SH (high doses of fatty acids, glucose, insulin, reactive oxygen species).
Here we present initial results on dermal fibroblast derivation and characterisation of iPS cells from both steatosis and non-liver disease patients as controls. Followed by the differentiation into hepatocytes, then comparative transcriptome and reverse phase protein array-based analysis of insulin signalling and drug metabolism pathways.

Poster Presentation Abstracts

Symposium III

From Genomics to Application

MYCN-DNA vaccine is effective against a MYCN overexpressing NB cell line in a syngeneic A/J mice model

Presenting Author: Alexander Stermann
Alexander Stermann (1), Nicole Huebener (1), Diana Seidel (1) and Holger N. Lode (1)

University Medicine of Greifswald, Department of Paediatric Hematology and Oncology; Greifswald, Germany

High-level expression of MycN protein, caused by amplification of the gene, characterizes the malignant phenotype of neuroblastoma (NB). Recent studies suggest that MycN is a suitable target for immunotherapy, but up to now, a syngeneic NB mouse model overexpressing MYCN is not available to examine immunotherapeutic strategies in vivo.
Here, we report the development of an MYCN overexpressing NXS2 NB cell line syngeneic to A/J mice. Stable transfection was verified by real-time PCR and Western-Blot analysis revealing high expression of MycN RNA and protein. Furthermore, a MYCN-DNA vaccine (pMDV1), based on epitopes encoding for three peptides from the murine MycN protein sequence with high affinity to the A/J mouse MHC class I allele H2-Kk, was designed and tested in vivo for its ability to induce an antigen-specific immune response.
We could show that tumor growth from the new cell line was significantly reduced in mice vaccinated with the pMDV1-vaccine compared to control groups. Furthermore, Lymphocytes isolated from vaccinated A/J mice effectively lysed NXS2-MYCN cells in cytotoxicity assays in contrast to wild type NXS2 cells and lymphocytes from control mice. Lymphocytes from vaccinated mice produced significantly higher amounts of IFN-γ after stimulation with irradiated NXS2 cells than lymphocytes from control mice. Interestingly, pMDV1 induced cytotoxic T lymphocytes also kill parental NXS2 tumor cells which show low MYCN expression, but the effect is enhanced with NXS2-MYCN cells.
In summary, we demonstrate the development of a new MYCN-DNA vaccine and a murine MYCN NB cell line syngeneic to A/J mice for in vivo evaluation of MycN directed immunotherapeutic strategies. In this model we show a significant reduction of tumor growth in MYCN vaccinated groups compared to control groups.

Kinase Networks in pancreatic cancer – Pyruvate kinase M2 and Protein kinase D2 as potential targets in pancreatic cancer

Presenting Author: Grit Rehbein
Grit Rehbein, Claudia Temme, Nancy Funk, Thomas Seufferlein

Department of Internal Medicine I, Martin-Luther-University Halle-Wittenberg, Germany

Protein kinases are differentially regulated in tumor cells. They regulate diverse biological functions such as proliferation, apoptosis, resistance, invasion and metastasis. Therefore they are major targets for drug development.
In microarray analysis, comparing normal against pancreatic tumor tissues, Pyruvate Kinase M2 (PKM2) has been found to be differentially expressed in pancreatic cancer. Moreover it is known that PKM2 plays an important role in cancer development. Thus PKM2 was selected as a candidate gene for further investigation. In this study PKM2 was found to positivly regulate tumor cell proliferation and migration. In addition we found opposing effects of PKM2 on tumor formation of Panc1 and MiaPaCa2 cells. Nevertheless we could show that downregulation of PKM2 leads to a more aggressive phenotype of MiaPaCa2- and PaCa3-cells.
In addition, PKM2 is a multifunctional protein which is involved in a variety of pathways and protein-protein interactions suggesting also multiple nonglycolytic functions. Thus, among others, focal adhesion kinase (FAK), which is present in adhesion structures within the cell, was identified as a potential substrate of PKM2 in a Kinase Substrate Identification Assay. Therefore we suggest that interaction of PKM2 and FAK could play an important role in the migration of pancreatic cancer cells.
Another kinase highly activated in tumor cells is the protein kinase D2 (PKD2). Depletion of PKD2 in pancreatic tumors inhibited angiogenesis and tumor growth in the chorioallantois model (CAM) and in orthotopic pancreatic cancer xenografts. PKD2 is identified as a potential target in pancreatic cancer so far. Therefore in cooperation with industrial partners we accomplished an inhibitor screen for PKD2.
PKM2 and PKD2 are multifunctional proteins which are involved in a variety of pathways and protein-protein interactions. Therefore it is important to look at the multiple possible effects of inhibiting PKM2 or PKD2 in pancreatic cancer.

DIPSBC - An XML based data integration platform for systems biology collaborations

Presenting Author: Felix Dreher
Felix Dreher (1), Christopher Hardt (1), Thomas Kreitler (1), Reha Yildirimman (1), Bodo Lange (1), Joachim Jankowski (2), Hans Lehrach (1), Ralf Herwig (1)

(1) Max Planck Institute for Molecular Genetics, Department of Vertebrate Genomics, Berlin

(2) Charité, Campus Benjamin Franklin, Universitätsmedizin Berlin

Modern biomedical research is often organised in collaborations sometimes involving dozens of labs worldwide. In particular, in genome research and systems biology complex molecular systems are under investigation that need the generation and interpretation of heterogeneous data for their explanation, for example ranging from gene expression studies and mass spectrometry measurements to experimental techniques for molecular interactions and functional assays.
Extensible markup language (XML) has become the most prominent way for representing and exchanging these data. However, besides the development of standards there is still a fundamental lack of data integration systems that are able to utilise these exchange formats, organise the data in an integrated way and link it with applications for data interpretation and analysis.
Here we present DIPSBC, Data Integration Platform for Systems Biology Collaborations, an interactive data integration architecture supporting collaborative research projects. All components of the system are open-source developments, and, thus, can be quickly adopted by researchers. An exemplary installation of such a collaboration platform is provided at http://dipsbc.molgen.mpg.de. DIPSBC is currently in use in five different collaborations projects such as the NGFN-plus projects MUTANOM, Modifiers and the NGFN-transfer project NT-CVD.

Prognostic and Predictive Relevance of Immunoglobulin Kappa C (IGKC)

Presenting Author: Cristina Cadenas
Cristina Cadenas (1), Marcus Schmidt (2), Birte Hellwig (3), Seddik K Hammad (1), Mathias Gehrmann (4), Patrick Micke (5), Jörg Rahnenführer (3) and Jan G Hengstler (1)

(1)Leibniz Research Centre for Working Environment and Human Factors (IfADo) at Dortmund TU, Germany

(2)Department of Obstetrics and Gynecology, University Hospital, Mainz, Germany,

(3)Department of Statistics, Technical University, Dortmund, Germany,

(4)Bayer GmbH, Leverkusen, Germany

(5)Dept. of Genetics and Pathology, Uppsala University, Uppsala, Sweden

Tumor-immune cell interactions and the role of infiltrating immune system cells in tumor progression are currently major issues of research. Recently, a strong prognostic impact of the humoral immune system on prognosis of breast cancer has been demonstrated. These findings have important implications since they may lead to improved prediction of prognosis and therapeutic concepts. However, reliable and validated markers are missing and the responsible cell types are unknown. We have previously published a 70 gene-based B-cell metagene that is representative of the humoral immune system. Here, we evaluate whether a single gene, immunglobulin kappa C (IGKC), can replace the B-cell metagene.

Gene array data of 1824 breast cancer patients (medically untreated as well as anthracycline-based chemotherapy), 1056 non-small cell lung cancer, 513 colorectal and 426 ovarian cancer patients as well as paraffin embedded tissue of 330 breast cancer patients were analyzed. Prognosis was analyzed with Cox regression, Kaplan-Meier analysis, Brier scores and meta-analyses.

We found that IGKC allows a similarly good prediction of prognosis as the B-cell metagene in medically untreated node-negative breast cancer [HR=0.81; P<0.001] and response to anthracycline-based chemotherapy [HR=1.41; P<0.001]. The association of IGKC with prognosis was observed in all breast cancer molecular subtypes (e.g. ER+, ER-, HER2+). The result was confirmed by qRT-PCR using RNA from paraffin embedded material and by immunostaining. Confocal fluorescence microscopy showed that IGKC was expressed by tumor-infiltrating plasma cells (TIP). Similar to breast cancer, IGKC was also associated with better prognosis in non-small cell lung and in colorectal cancer but not in ovarian cancer.

In conclusion, IGKC is expressed by TIP and has independent prognostic and predictive impact in breast, lung and colorectal cancer.

ANALYSIS PIPELINE, VARIANT DATABASE AND LIMS FOR EXOME SEQUENCING DATA

Presenting Author: Thomas Wieland
Thomas Wieland (1), Sebastian H. Eck (1), Elisabeth Graf (1), Anna Benet-Pagès (1), Thomas Meitinger (1), Tim M. Strom (1)

(1) Institute of Human Genetics, German Research Center for Environmental Health, Munich, Germany

Enrichment techniques for targeted sequencing of coding regions are currently applied to identify rare variants. We developed a pipeline to analyze exome sequencing data and a database to store all variant data. The pipeline is a combination of Perl scripts and public available software packages (BWA, SAMtools). Identified variants are automatically annotated. Annotation includes presence in dbSNP, HGMD and the 1000 Genomes data as well as functional impact on the corresponding protein. The database can be queried through a web interface using standard queries. Exomes of individuals with other diseases are used as controls. The database has an interface to our LIMS which organizes the workflow from library prep to completed analysis. Barcoded tubes are used for sample tracking.
We applied the analysis pipeline to ~350 exomes. Sequencing of 10-11 GB results in a read depth of at least 20 for ~90% of the sequences. The pipeline calls ~21,000 coding variants. Approximately 10,000 of these are non-synonymous variants, ~150 variants affect canonical splice sites and ~400 are coding indels. We quantified the amount of new, putatively deleterious variants listed in the Human Gene Mutation Database (HGMD), and assessed the frequency of literature-annotated disease mutations. We identified 46 new heterozygous nonsense variants. 204 of HGMD annotated mutations (~0.75%) had a frequency of >2% in our samples. After subtracting these mutations with an unlikely high frequency, the carrier burden of recessive mutations from HGMD in these genes is between 0 and 12 per individual (average 3.6).
Additionally, we determined the distribution of non-synonymous variants per gene for OMIM and non-OMIM genes. The number of variants are normalized to 1000 aa. The normalized values do not differ between OMIM (15) and non-OMIM (16) genes. Genes with an excess of variants are identified and can be excluded from the analysis of rare variants.

Impact of common regulatory single nucleotide variants on gene expression profiles in whole blood

Presenting Author: Katharina Heim
Katharina Heim (1), Divya Metha (1,2), Gertrud Eckstein (1), Christian Gieger (3), Thomas Illig (3), Thomas Meitinger (1,4), Holger Prokisch (1,4)

(1) Helmholtz Center Munich, Neuherberg, Institute of Human Genetics

(2) Max Planck Institute, Munich, Institute of Psychiatry

(3) Helmholtz Center Munich, Neuherberg, Institute of Epidemiology

(4) Technical University Munich, Munich, Institute of Human Genetics

Genome-wide association studies (GWAS) have allowed the identification of susceptibility loci influencing a wide range of complex diseases and quantitative traits. Most of the identified SNPs, however, do not alter protein sequence and the majority of variants is located in regions with unknown functionality. A major challenge is the functional interpretation of GWAS results. Integration of functional data such as gene expression data with genotypic data allows prioritization of positional candidate genes, thereby providing a functional handle.
Most of human eQTL studies have analyzed single cell types such as lymphocytes or transformed lymphoblast cell lines while only rarely has whole blood been probed. There is currently a high interest in cataloguing eQTL data from a wider variety of tissues in order to uncover the tissue-specific proportion of eQTLs.
The aims of our study were threefold – (i) to test the value of whole blood in the detection of eQTLs in humans, (ii) to analyze if these eQTLs were robust and reproducible across different populations, and (iii) to elucidate whether whole blood eQTLs allow the identification of putative functional variants involved in the etiology of complex traits. To achieve this, whole blood expression levels of 41,409 transcripts (Illumina WG-6 v2) were interrogated for their associations with 335,152 autosomal SNPs (Affymetrix 500K) in 322 individuals from an explorative sample within the population-based KORA survey F3. 322 cis- and 32 trans- eQTLs were identified. The mean explained expression variance was 19% for cis- and 36% for trans-SNPs respectively.
We also examined if SNPs reported in GWAS of complex traits were significantly associated with whole blood RNA levels. We systematically tested all SNP-gene combinations of the NHGRI (National Human Genome Research Institute) GWAS catalog and identified 35 SNPs which were associated with the expression level of the nearby transcript.

Comprehensively Haplotype-Resolved German Genomes

Presenting Author: M.R. Hoehe
E.-K. Suk (1), G.K McEwen (1), J. Duitama (1), K. Nowick (1), S. Palczewski (1), S. Schulz (1), H. v. Eberstein (2), S. Schreiber (2), T. Hübsch (1), M.R. Hoehe (1)

(1) Max Planck Institute for Molecular Genetics, Berlin, (2) University of Kiel, IKMB, Kiel, Germany

Independent determination of both haplotype sequences of an individual genome is essential to relate genetic variation to genome function, phenotype and disease. Here we present the most complete haplotype-resolved genome to date, 'Max Planck One' (MP1), with virtually all SNPs (> 99%) and 80,000 indels phased into haploid sequences of up to 6.3 Mb (N50 ~1 Mb). This also represents the first German genome. To this end, we have developed & applied a fosmid pool-based next generation sequencing approach. The completeness of phasing allowed determination of the concrete molecular haplotype pairs for 81% of autosomal protein-coding genes including regulatory sequences (up to ~ 5.7 Mb), of which over 90% were found to be constituted by two different molecular forms. A subset of 159 genes with potentially severe mutations in either cis or trans configurations highlighted in particular the role of phase for gene function, disease, and clinical interpretation of genomes. Extended genomic regions harboring manifold combinations of physically and/or functionally related genes and regulatory elements were resolved into their underlying 'haploid landscapes', which may define the functional genome. Importantly, we have resolved haplotypes across the MHC region, demonstrating an application of phase of key clinical relevance for transplantation success. With > 10,000 genetic differences between MP1's extended MHC haplotypes identified, exploration of novel genetic determinants for severe GvHD & many other diseases becomes now feasible. Our work provides the foundation to understand that the distinction of molecular haplotypes is essential to resolve the (inherently individual) biology of genes, genomes and disease, establishing a reference point for 'phase-sensitive' personal genomics. We have moreover haplotype-resolved a HapMap trio child & many more German genomes, thus validating our approach, setting a new gold-standard and advancing diploid genomics to the population level.

Screen for iron homeostasis in N-ethyl-N-nitrosourea-treated mice resulted in mutant lines with increased plasma ferritin levels

Presenting Author: Bernhard Aigner
Birgit Rathkolb (1), Martina Klempt (1), Sibylle Wagner (2), Dian Michel (2), Matthias Klaften (2), Jürgen Laufs (3), Boris Schneider (3), Reinhard Sedlmeier (3), Martin Hrabé de Angelis (2), Eckhard Wolf (1), Bernhard Aigner (1)

(1) Chair for Molecular Animal Breeding and Biotechnology, Department of Veterinary Sciences, and Laboratory for Functional Genome Analysis (LAFUGA), Gene Center, LMU Munich, Munich, Germany

(2) Institute of Experimental Genetics, Helmholtz Zentrum München, Neuherberg, and Chair for Experimental Genetics, TU Munich, Freising-Weihenstephan, Germany

(3) Ingenium Pharmaceuticals, Martinsried, Germany

Iron is essential for various cellular processes. Analysis of iron homeostasis in patients is carried out by clinical chemical blood analysis including ferritin and transferrin as commonly used parameters. Here, we retrospectively evaluated the use of plasma ferritin, transferrin and iron in the phenotype-driven Munich N-ethyl-N-nitrosourea (ENU) mouse mutagenesis project as parameters for the generation of novel animal models for human diseases. The clinical chemical blood analysis was carried out on more than 10,000 G1 and G3 offspring of chemically mutagenized inbred C3H mice to detect dominant and recessive mutations leading to deviations in the chosen plasma parameter levels. We identified animals consistently exhibiting altered plasma ferritin or transferrin values. Transmission of the phenotypic deviations to the subsequent generations led to the successful establishment of mutant lines for the parameter ferritin. Successful linkage analysis was carried out for the mutant lines FER001 and FER002 suggesting Fth1 as candidate gene for the causative mutation in both lines. In line FER001, sequence analysis of Fth1 detected a point mutation leading to an amino acid exchange. Thus, novel mouse models for the functional analysis of iron homeostasis were established by a phenotype-driven screen for mutants.

German Mouse Clinic - Why do Emory mice develop cataracts?

Presenting Author: Birgit Rathkolb1,2
Birgit Rathkolb (1,2), Kateryna Micklich (2), Cornelia Prehn (2), Jerzy Adamski (2), Patricia da Silva-Buttkus (3), Frauke Neff (3), Valerie Gailus-Durner (2), Helmut Fuchs (2), Jochen Graw (4), Martin Hrabé de Angelis (2), Eckhard Wolf (1)

(1) Ludwig-Maximilians-Universität München - Munich, Chair of Molecular Animal Breeding and Biotechnology,

(2) Helmholtz-Zentrum München - Munich, Institute of Experimental Genetics

(3) Helmholtz-Zentrum München - Munich, Institute of Pathology

(4) Helmholtz-Zentrum München - Munich, Institute of Developmental Genetics

The Emory mouse is a spontaneous mouse mutant representing a model of inherited senile cataract, which was described the first time about 30 years ago (Kuck et al. 1981-1982). In the mean time several studies on lenses of Emory mice have been carried out to characterize cataract development, but the genetic causes underlying this phenotype still remain to be discovered. Preliminary results suggest that mutations in at least two genes contribute to the mutant phenotype (personal communication). We have conducted a complete GMC Primary screen (Fuchs et al. 2011) and a selection of secondary investigations on Emory mice in order to elucidate the pathogenesis causing cataract formation in this mutant mouse strain. Inbred Emory mice have been compared to CFW wild-type mice, representing the genetic background of Emory mice. We detected changes in plasma electrolyte concentrations, increased plasma urea and cholesterol levels and decreased activities of alpha-Amylase and alkaline phosphatase in the primary screen. Secondary investigations revealed changes in kidney function and several endocrinological parameters. Our results indicate that cataracts in Emory mice are a late onset symptom of a disorder affecting electrolyte and water balance, which is due to endocrinological changes and/or renal dysfunction.

Monitoring of volatile organic compounds for metabolic phenotyping in mice

Presenting Author: Jan Rozman
Jan Rozman (1,2), Martin Kistler (1), Wilfried Szymczak (3), Christoph Hoeschen (3), Martin Klingenspor (2), Martin Hrabê de Angelis (1)

(1) Institut für Experimentelle Genetik, Helmholtz Zentrum München

(2) Molekulare Ernährungsmedizin, ZIEL und Else Kröner Fresenius Center, Technische Universität München

(3) Abteilung für Medizinische Strahlenphysik und Diagnostik, Helmholtz Zentrum München

Volatile organic compounds (VOCs) originating from metabolic processes circulate in the blood, are exchanged between blood and the volume of the lungs and are finally exhaled during gas exchange. When collected under standardized conditions, VOCs can be specific markers for diseases. Non-invasive breath gas analysis for VOCs is applied in human studies (e.g. on metabolic disorders or cancer) but is uncommon in mouse studies even though the phenotyping of mouse models for human disorders is of high relevance in genome research. In a collaborative project in the German Mouse Clinic (GMC) involving researchers from physiology, physics, nutrition and bio-mathematics we developed a novel approach for the analysis of VOCs in unrestrained mice analyzing accumulation profiles by proton transfer reaction mass spectrometry (PTR-MS). The innovative approach is composed of a 4-step strategy: (1) sorting out profiles disturbed by environmental confounders, (2) identification of VOCs originating from exhaled breath, (3) determination of the source strength of VOCs and (4) adjusting the source strength to activity levels strongly affecting exhaled minute volume. In proof of principle experiments, C57BL/6J mice and New Zealand Obese mice were fed a high fat diet. The dietary intervention resulted in significant alterations in VOCs which could be related both to metabolic pathways and to effects of gut microbiota. The novel online analysis of VOCs has a high potential for mouse phenotyping, challenge studies and drug testing. A PTR-MS with time of flight detection (PTR-TOF-MS) recently installed in the GMC will be used for the screening of mouse mutants for metabolic phenotypes, and to monitor specific VOCs that were identified and validated as biomarkers for metabolic disorders. The TOF system with its high sensitivity, measurement speed, and mass resolution can detect these biomarkers at low concentrations during early pathogenesis or early responses to treatment.

MVD013 a mouse model of inherited polycythaemia.

Presenting Author: Kateryna Micklich
Kateryna Micklich(1), Thure Adler(2,1), Dirk Busch(2), Juan Antonio Aguilar Pimentel(5,1), Sibylle Wagner(1), Monica Tost(3,1), Julia Calzada-Wack(3,1), Irene Esposito(3), Helmut Fuchs(1), Valérie Gailus-Durner(1), Bernhard Aigner(4), Martin Hrabé de Angelis(1), Eckhard Wolf(4), Birgit Rathkolb(4,1)

(1) Institute of Experimental Genetics, German Mouse Clinic, Helmholtz Zentrum München,

(2) Institute for Medical Microbiology, TU München,

(3) Institute of Pathology, Helmholtz Zentrum München,

(4) Chair of Molecular Animal Breeding and Biotechnology, LMU,

(5) Department of Dermatology and Allergy, Biederstein, TU München

MVD013, a mutant mouse line showing a dominantly inherited polycytemia phenotype in the peripheral blood cell count, was established within the Munich ENU mouse mutagenesis project by the Clinical Chemistry Screen. Additionally, gastrointestinal tumors are found at the ileum and caecum of almost all aged mutant mice. SNP analysis and additional fine mapping showed the highest possibility of the mutation to be located on chromosome 5. We sequenced the most promising candidate genes Kdr, c-Kit and Pdgfr-a. The latter two genes are associated with gastro-intestinal stromal tumors (GIST) and myeloproliferative disorders. Kdr coding for the vascular endothelial growth factor receptor is essential for the differentiation of hematopoietic precursors and is associated with several kinds of cancers. Our results show that these three genes do not have a mutation in the coding part of the gene and in promoter regions of c-Kit and Pdgfr-a genes. A comprehensive phenotypic characterization of this mouse line by the German Mouse Clinic (1) identified additional effects on the distribution of leucocyte subsets in peripheral blood and the cardiovascular system as well as gastro-intestinal function and pathology. On the basis of additional analyses such as measurement of erythropoietin level in plasma, blood gas analysis, differential white blood cell count and other tests carried out in several collaborations we get a complex phenotype picture of this mutant mouse line. Since MVD013 shows similar symptoms like human patients suffering from Polycythemia Vera (PV) or Gastrointestinal stromal tumors (GIST) it might represents a model that can be used to elucidate regulatory mechanisms that may play a role in the development of GISTs or polycythemias in humans.

(1)Gailus-Durner et al. (2009): The German Mouse Clinic: a platform for systemic phenotype analysis of mouse models. Curr. Pharm Biotechnol 10 (2): 236-243

German Mouse Clinic - Reduced Tom40 expression in mice leads to mitochondrial dysfunction

Presenting Author: Lore Becker (1,2)
Ramona Zeh (1,2), Lore Becker (1,2), Andreas Bender (2), Thomas Floss (4), Anja Schrewe(1), Julia Calzada-Wack (6), Frauke Neff (6), Lillian Garrett (4), Sabine Hölter (4), Helmut Fuchs (1), Valerie Gailus-Durner (1), Raffi Bekeredjian (5), Thomas Meitinger (4), Wolfgang Wurst (4), Holger Prokisch (3), Thomas Klopstock (2) , Martin Hrabé de Angelis (1)

(1) Institute of Experimental Genetics, Helmholtz Zentrum München, German Research Center for Environment and Health, Neuherberg, Germany

(2) Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-Universität, Ziemssenstr.1a, 80336 Munich, Germany

(3) Institute of Human Genetics, Helmholtz Zentrum München, German Research Center for Environment and Health, Neuherberg, Germany

(4) Institute of Developmental Genetics, Helmholtz Zentrum München, German Research Center for Environment and Health, Neuherberg, Germany

(5) Internal Medicine III, University of Heidelberg, Im Neuenheimer Feld 410, Heidelberg, Germany

(6) Institute of Pathology, Helmholtz Zentrum München, German Research Center for Environment and Health, Neuherberg, Germany

Mitochondria play a pivotal role in generating cellular energy from nutrient fuels. The vast majority of mitochondrial proteins is encoded by nuclear genes and then imported into the organelle. By gene trap mutagenesis, we have created a knockout mouse model for the Translocase of the outer membrane (Tom) 40, the key component of the general import pore. Phenotypic analysis of Tom 40 mice was performed in the German Mouse Clinic (GMC). Homozygous Tom40-/- mice are not viable. Heterozygous Tom40 +/- mice.showed cardiac impairment with prolonged Q-T and S-T interval already in young animals. Hearts of these mice displaced altered morphology of muscle fibers and altered ultrastructure of mitochondria. Analysing neurological functions in young mice revealed increased PPI and small alterations in motor coordination. Motor deficits become more pronounced with increasing age indicated by impaired rotarod performance. Functional assessment of mitochondria performed with polarographic measurement of respiratory chain complexes of heart mitochondria showed decreased Comlex IV activity especially in old mutant mice.
We conclude that heterozygous Tom 40 mice can compensate reduced levels of Tom40 to a great extend in young animals but show more clinical phenotypes in older mice. This model is a valuable tool for the analysis of age-related decline of mitochondria function and might as well be considered as a candidate for screening human patients with mitochondrial diseases.

Requirement of the RNA editing enzyme ADAR2 for normal physiology in mice

Presenting Author: Marion Horsch
Marion Horsch (1), Peter H. Seeburg (2), Thure Adler (3), Juan Antonio Aguilar-Pimentel (4,5), Lore Becker (6), Julia Calzada-Wack (7), Lilian Garrett (8), Alexander Götz (9), Wolfgang Hans (1), Miyoko Higuchi (2), Sabine M. Hölter (8), Beatrix Naton (1), Cornelia Prehn (1), Oliver Puk (8), Ildikó Rácz (10), Birgit Rathkolb (11), Jan Rozman (12), Anja Schrewe (1,13), Jerzy Adamski (1,14), Dirk H. Busch (3), Irene Esposito (7,15), Jochen Graw (8), Boris Ivandic (13), Martin Klingenspor (12), Thomas Klopstock (6), Martin Mempel (4,5,16), Markus Ollert (4), Holger Schulz (9,18), Eckhard Wolf (11), Wolfgang Wurst (8,17,19,20), Andreas Zimmer (10), Valérie Gailus-Durner (1), Helmut Fuchs (1), Martin Hrabe de Angelis (1,14), Johannes Beckers (1,14)

(1) Institute of Experimental Genetics, Helmholtz Zentrum München,

(2) Departments of Molecular Neurobiology and Cell Physiology Heidelberg, (3) Institute for Medical Microbiology, Immunology, and Hygiene TU München, (4) Clinical Research Division of Molecularand Clinical Allergotoxicology, TU München, (5) Division of Environmental Dermatology and Allergy TU München, (6) Department of Neurology LMU München, (7) Institute of Pathology, Helmholtz Zentrum München, (8) Institute of Developmental Genetics, Helmholtz Zentrum München, (9) Comprehensive Pneumology Center, Helmholtz Zentrum München, (10) Institute of Molecular Psychiatry, University of Bonn, (11) Chair for Molecular Animal Breeding and Biotechnology, LMU München, (12) Molecular Nutritional Medicine, TU München, (13) Department of Medicine III, University of Heidelberg, (14) Chair of Experimental Genetics, TU München, (15) Institut für Allgemeine Pathologie und Pathologische Anatomie am Klinikum rechts der Isar, TU München, (16) Department of Dermatology, Venerology, and Allergy, Universität Göttingen, (17) Chair of Developmental Genetics, TU München, (18) Institute of Epidemiology I, Helmholtz Zentrum München, (19) MPI für Psychiatrie, München, (20) Deutsches Zentrum für Neurodegenerative Erkrankungen, München

ADAR2, an RNA editing enzyme that converts specific adenosines to inosines (A-to-I editing) in certain pre-mRNAs, often leads to amino acid substitutions in the encoded proteins. The enzyme is mainly expressed in brain. Of all ADAR2-mediated edits, a single one in the pre-mRNA of the AMPA receptor subunit GluA2 (Q/R site) is essential for survival. Hence, early postnatal death of mice lacking ADAR2 (ADAR2-/-) is averted when the critical edit is engineered into both GluA2 encoding Gria2 alleles GriaR/R). Adar2-/-/Gria2R/R mice display normal appearance and life span, but the systemic phenotypic effects of global lack of ADAR2 have remained unexplored. Thus, to gain further insights into the physiological relevance of ADAR2 edits excepting the Q/R site, we systematically analyzed the phenotype of the double mutant mouse line, employing GriaR/R mice as controls, in the German Mouse Clinic (GMC) by determining approximately 320 parameters. This comprehensive phenotypic analysis of the Adar2-/-/Gria2R/R mice revealed several specific mutant phenotypes such as changes in behavior, hearing ability, allergy parameters and gene expression profiles in the brain. These results now provide a rational basis for targeted studies of ADAR2 functions and for the identification of new functional ADAR2 targets.

The European Mouse Mutant Archive (EMMA)

Presenting Author: Michael Hagn
Michael Hagn (1), Marschall Susan, Fessele Sabine, Hrabé de Angelis Martin

Helmholtz Zentrum München, Institute of Experimental Genetics (HMGU-IEG), Neuherberg, Germany

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 14 partners who operate as the primary mouse repository in Europe and is funded by the participating institutes and the European Commission FP7 Capacities Specific Program.

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.

Findings from the Vision Screen of the German Mouse Clinic

Presenting Author: Oliver Puk
Oliver Puk (1), Minxuan Sun (1), Jack Favor (2), Claudia Dalke (3), Martin Hrabé de Angelis (4), Jochen Graw (1)

(1) Helmholtz Zentrum München, Institute of Developmental Genetics

(2) Helmholtz Zentrum München, Institute of Human Genetics

(3) Helmholtz Zentrum München, Institute of Radiation Biology

(4) Helmholtz Zentrum München, Institute of Experimental Genetics

The German Mouse Clinic (GMC) is a large scale phenotyping center where mouse models for human diseases are analyzed in a standardized way. More than 550 parameters are investigated by mouse researchers and clinicians from various fields with the objective of improving knowledge about molecular mechanisms of these disorders and enabling development of new therapies.
Within the GMC, the Vision Screen characterizes changes in the eye and its major tissues, the cornea, the lens, the retina and the optic nerve. In the Primary Vision Screen, we identify alterations using a broad variety of non-invasive techniques like Slit Lamp Biomicroscopy (general appearance of the eye and transparency of the cornea and lens), Funduscopy (to detect changes in the retina), and Laser Interference Biometry (for various eye size parameters). Recently, we established modern systems to optimize standard investigations. The novel Scheimpflug imaging system enables us to quantify cornea and lens opacities, the Optical Coherence Tomography gives a non-invasive histological picture of the retina, and the Virtual Drum allows a functional analysis of the eye and the entire visual system. In the Secondary Vision Screen, we use Electroretinography for a functional characterization of the retina.
Since the start of the GMC, approximately 200 mutant lines have been investigated. 22 of these mutants showed significant changes in the eye. We here give an overview of the most interesting pathologic findings in the Primary and Secondary Vision Screen including cataract formation (mutant line Cap2), optic nerve head degeneration (Bmpr1b), and microphthalmia (Aspm). We further present first results obtained with the novel Scheimpflug imaging system and Optical Coherence Tomography, demonstrating that these techniques represent suitable tools for high-throughput analysis of the mouse eye.

Inbred wild type mouse lines have distinct spontaneous morphological phenotypes

Presenting Author: Raisa Serpi
Raisa Serpi (1), Tanja Klein-Rodewald (1), Julia Calzada-Wack(1), Frauke Neff(1), Valérie Gailus-Durner(2), Helmut Fuchs(2), Martin Hrabé de Angelis(2) and Irene Esposito(1)

(1)Institute of Pathology, Helmholtz Zentrum München, German Research Center for Environmental Health, 85764 Neuherberg, Germany

(2)Institute of Experimental Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, 85764 Neuherberg, Germany

The mouse is the most commonly used animal for modelling human diseases. New approaches to generate genetically manipulated mouse models representing human diseases as well as target the function of specific genes has increased the importance of mice in biomedical science. For the correct interpretation of alterations in mouse phenotype the basic morphology of background mouse lines must be known. Although there are on-going efforts to create publicly available baseline phenotypic data, for now the information concerning spontaneous lesions in wild-type mice is incomplete and scattered, and further studies are needed. We addressed this problem by screening haematoxylin-eosin stained sections of brain, reproductive organs, urinary bladder, thyroid, parathyroid, heart, lung, kidney, liver, spleen, thymus, lymph nodes, adrenal glands, stomach, intestine, skin and pancreas for inherent spontaneous morphological lesions of 17-23 week old animals of six commonly used inbred mouse lines; C57Bl6J, C57BlN, C3HeB/FeJ, Balb/cByJ, 129P2OlaHsd and FVB/N. We found hepatocellular necrosis in female FVB/N mice, and increased hepatic steatosis in Balb/cByJ male mice. Lipomatosis in pancreas was apparent in both genders of FVB/N mice and in female C3HeB/FeJ mice. Subcapsular cell hyperplasia in adrenal cortex is a common phenomenon, which was evident in almost all wild type mouse strains. Lymphatic tissue in lungs (BALT) and intestines (Peyer's pathes) was mostly seen in Balb/cByJ and C3HeB/FeJ mice. We also observed high incidence of epicardial calcifications in hearts of Balb/cByJ mice. We discuss the importance of these findings for interpretation of results from studies using genetically manipulated mice. Care should be taken when choosing the background mouse line for genetic manipulations, since different mouse lines harbour different inherent lesions which can affect the function of targeted genes, interpretation of results and translation of results to model human disease.

The Pathology Screen within the GMC: yesterday, today, tomorrow

Presenting Author: Tanja Klein-Rodewald (1)
Julia Calzada-Wack (1),Ilona Moosbrugger (6), Gaby Hölzlwimmer (5), Sandra Kunder, Tanja Klein-Rodewald (1), Eva Janas (1),Martin Hrabé de Angelis (3), Helmut Fuchs (3), Valerie Gailus-Durner (3),Ireme Esposito (2) Letitia Quintanilla-Martinez (4),Helmut Höfler (1,2,), Frauke Neff (1)

(1) Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Pathology, Munich, Germany

(2) Technische Universität München, Institute of Pathology and Pathological Anatomy, Munich, Germany

(3) Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Experimental Genetics, Munich, Germany

(4)Eberhard Karls University, Institute of Pathology, Tübingen, Germany

(5) Roche Company, Penzberg, Germany

(6) Sanitätsakademie der Bundeswehr, Neuherberg, Germany

History
Originated from the laboratory for analysis of trial animals, that was funded in the department at the former GSF; the mouse pathology group is participating as primary screen in the German Mouse Clinic since 2002. Prior and after the participation in the GMC, always a human pathologist was part of the staff members to provide a translational approach between trial animals and human diseases. Due to the large numbers of mice that have been analyzed the mouse pathology group gained and provides a broad expertise in mouse anatomy and pathology. Undisputed is the knowledge about common findings in various inbred and backcrossed background strains and mutation associated phenotypes. Under the direction of Dr. L. Quintanilla-Martinez, the mouse pathology laboratory established systematically in rodent tissue an antibody panel for immunohistochemistry comparable to a human pathology panel. This is still ongoing and, together with image analysis, electron microscopy, and molecular pathological analysis serves as an excellent platform for in-depth analysis of mice mutants. Examples of the analyzed mouse lines and schematic representation of the flow and results (heat map) are shown.

Conclusion
The histopathological phenotyping of the mutant mice plays therefore a valuable role in a multidisciplinary effort to identify and characterize anatomical changes introduced by the mutation of interest and ultimately establish a relation to human diseases.

German Mouse Clinic – proportions of leukocyte subsets in peripheral blood as genetic trait in mice: lessons from studies of strain-dependent differences

Presenting Author: Thure Adler (1,2)
Thure Adler (1, 2), Admar Verschoor (2), Valerie Gailus-Durner (1), Helmut Fuchs (1), Martin Hrabê De Angelis (1), Dirk H Busch (2)

(1) Helmholtz Zentrum München - Neuherberg, Institute for Experimental Genetics, German Mouse Clinic

(2) Technische Universität München- Munich, Institute for Medical Microbiology, Immunology and Hygiene

Inbred strains are known to differ in the frequencies of leukocyte subsets in lymphoid organs and in peripheral blood. Moreover, several CD antigens are restricted to specific mouse strains or interstrain differences occur concerning the level of expression of certain CD antigens. To test this, we compared flow cytometric phenotyping data from several cohorts of 129 and C57BL/6 mice. By hierarchical cluster analysis, using a set of leukocyte subset frequencies as vector, a complete discrimination of two strain-specific clusters was achieved. We evaluated the subset of L-selectin expressing T cells, which had shown strong differences in frequencies between 129 and C57BL/6. Our studies demonstrate 1) that the frequency of L-selectin expressing T cells decreases upon red cell lysis; 2) that the grade of L-selectin loss on T cells is a strain specific trait; T cells from 129 are far more sensitive to red cell lysis than T cells from C57BL/6 mice. Our findings have implications for our interpretation of phenotyping results.
Exemplarily, we present data from one knockout mouse line generated in 129 and subsequently backcrossed into C57BL/6, where we found the 129 phenotype of red cell lysis induced L-selectin loss retained. By analysing a further mutant line targeting the same gene we exclude a k.o.-gene related phenotype. We conclude that 129-specific gene variants might cause specific immunological phenotypes in mouse mutant lines which originate from 129 ES cells.

GERMAN MOUSE CLINIC - NEW MOUSE MODELS AND MECHANISMS FOR BONE AND CARTILAGE DISORDERS

Presenting Author: Wolfgang Hans
Wolfgang Hans (1), Christian M Cohrs (1), Koichiro Abe (2), Valerie Gailus-Durner (1), Helmut Fuchs (1), Martin Hrabé de Angelis (1)

(1) Helmholtz Center Munich, German Research Center for Environmental Health GmbH, Institute of Experimental Genetics, Neuherberg, Germany

(2) Tokai University Medical School, Basic Medical Science and Molecular Medicine, Kanagawa, Japan

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/osteoclast cell culture system to describe potential cellular causes of bone diseases.
Since the beginning of the GMC the Core Facility provided 208 mutant mouse lines for the primary screen. Most of the mutant lines have already finished the phenotypic analysis in the Bone and Cartilage module. In 34 mutant lines, a bone specific phenotype was known before the GMC screen, and we could confirm all of them. In 29 lines out of the 34 lines, we were able to detect additional phenotypes. In 48 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. We recently published the Ali14 mouse mutant line, a new mouse model for inflammatory arthritis. A novel missense/gain-of-function mutation in the phospholipase Cγ2 gene (Plcg2) resulted in swollen and inflamed hind paws, reduced bone mineral contents/density, and various metabolic defects.
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 environmental challenge platform, we established an activity challenge to test genotype-envirotype interactions on bone health. First results of the treadmill challenge showed that physical activity and the genetic background have an influence on bone health in mice.

Inhibitory effect of Mg^{2+} on phosphate-induced vascular calcification in CKD patients

Presenting Author: Joachim Jankowski
Silvia Salem1), Heike Bruck2), Ferdinand H. Bahlmann3), Axel Kretschmer4), Michaela Volsek2), Andreas Kribben2), Vera Jankowski1), Joachim Jankowski1)

1) Charité, Med. Clinic IV, University of Berlin, Germany

2) Universitätsklinikum Essen, Essen, Germany

3) Universitätsklinikum Homburg, Germany

4) Bayer Health Care AG, Wuppertal, Germany

BACKGROUND: Arteriosclerosis and cardiovascular disease of chronic kidney failure (CKD) patients are strongly associated with vascular calcification. This study focuses on the effect of mag-nesium ion (Mg^{2+}) on vascular calcification. Furthermore, plasma Mg^{2+} concentrations were asso-ciated with parameters of vascular calcification in vivo.

METHODS: Aortic rings of Wistar rats were incubated in absence and presence of $MgCl_2$ and phosphate concentration of the medium was elevated. Serum Mg^{2+} concentrations of CKD patients were associated with intima-media-thickness (IMT) and aortic pulse wave velocity (PWV) as sur-rogate parameter for arteriosclerosis and arterial stiffening.

RESULTS: Incubation of aortic rings in the presence of BGP and NaH_2PO_4 caused an increased tissue-Ca^{2+}-deposition compared to control conditions (BGP: 115.7 ± 11.2 vs. 87.0 ± 8.5; NaH_2PO_4: 107.2 ± 10.3 vs. 87 ± 8.5; each in nmolCa^{2+}/mgtissue; n=6). This increased amount of Ca^{2+}-amount in the aortic rings was significantly decreased in the presence of Mg^{2+} (83.6 ± 7.3 and 70.4 ± 10.48 nmolCa^{2+}/mgtissue). In CKD patients, but not in controls, magnesium serum concentration was associated with the IMT (IMT_{left}: 0.97 ± 0.07 vs. 0.78 ± 0.05; IMT_{right}: 0.93 ± 0.08 vs. 0.74 ± 0.04 (mm; normal vs. high Mg^{2+} range). In addition, CKD patients with higher magnesium serum concentration had a significant lower PWV.

DISCUSSION AND CONCLUSION: Elevated phosphate concentrations induce in vitro medial calcification. Mg^{2+} ions reduced in vitro vascular calcification despite increased phosphate concen-tration. This hypothesis is additionally based on the fact that CKD patients with high Mg^{2+} serum levels had significantly lower IMT and PWV values, which may result in a lower risk for cardio-vascular events and mortality in these patients. Therefore, Mg^{2+} supplementation may be an option for treatment and prevention of vascular calcification resulting in a reduction of cardiovascular events in CKD patients.

Identification of the strongest MAS-agonist

Presenting Author: Joachim Jankowski
Vera Jankowski1), Markus Tölle1), Robson A. S. Santos2), Michael Bader3), Axel Kretschmer4), Walter Zidek1), and Joachim Jankowski1)

1) Charité-Universitätsmedizin Berlin (CBF), Medizinische Klinik IV, Germany

2) Department of Physiology and Biophysics, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

3) Max-Delbrueck-Center for Molecular Medicine, Berlin, Germany

4) Bayer-Schering Pharma, BSP-GDD-GTR-TD-BIO2, Wuppertal, Germany

The family of angiotensin peptides has been steadily growing in recent years. Most are fragments of angiotensin II (Ang-II) with different affinities to the known angiotensin receptors. Here we describe the novel endogenous octapeptide Pro-Glu-Val-Tyr-Ile-His-Pro-Phe (Angioprotectin), which acts as a strong agonist at MAS receptors. Angioprotectin provides physiological antagonism of vasoconstrictor actions of Ang-II via the AT1 and MAS receptor. Plasma concentrations in healthy human volunteers were about 15 % and in renal failure patients up to 50 %, of plasma Ang-II concentrations. A commercially available Ang-II anti-body did not discriminate between Angioprotectin and Ang-II and thus Angioprotectin can contribute to Ang-II concentrations measured by antibody-based assays. This novel peptide is likely to be a relevant component of the human renin-angiotensin-system.

Oxidative stress in chronic kidney disease

Presenting Author: Joachim Jankowski
Anna Marta Schulz, Vera Jankowski, Walter Zidek and Joachim Jankowski

Charité-Universitätsmedizin Berlin (CBF), Medizinische Klinik IV, Germany

Background: A number of cardiovascular diseases is characterized by increased concentration of reactive oxygen species (ROS). However, the link between genesis of cardiovascular complications, uremic toxicity and increased oxidative stress in patients with chronic kidney disease is not well-understood until now.
In this study, we investigated the effect of seventy eight known and commercial available uremic toxins on the enzymatic activity of the lymphocytic NADPH oxidase in this study.
Methods: Lymphocytes were isolated, lysed and incubated with NADPH in the presence and absence of the uremic toxin of interest. The degradation of NADPH by the lymphocytic NADPH oxidase was quantified. Additionally, we investigated the effects of plasma on the NADPH oxidase activity.
Results: Thirty nine of seventy eight known uremic toxins showed an effect on the NADPH oxidase activity. Thirty five of the uremic toxins decreased the NADPH oxidase activity. Orotic acid has been characterized as the strongest inhibitor of the NADPH oxidase. Four of the investigated uremic toxins increased the NADPH oxidase activity. SDMA showed the strongest stimulating effect. Plasma from CKD patients before dialysis and the resulting hemofiltrate showed a significant inhibitory effect on the NADPH oxidase activity. Plasma after dialysis did not show any effect on the NADPH oxidase activity.
Discussion: Uremic toxins with stimulating effect on the NADPH oxidase activity seem to contribute to cardiovascular disease directly. On the other hand the inhibitory uremic toxins may fulfil a direct protective function in the development of the cardiovascular damage in patients with renal failure.
Conclusions: The results of the study demonstrate that uremic toxins may play an important role in the pathogenesis of the cardiovascular complications in chronic kidney disease by modulation of the NADPH oxidase activity.

In patients with chronic kidney disease resistin correlates with markers of tissue injury response but not with markers of inflammation

Presenting Author: Axel Kretschmer
Axel Kretschmer (1), Michaela Volsek (2), Andreas Götte (1), Thomas Krahn (1), Andreas Kribben (2), Heike Bruck (2)

(1) Bayer HealthCare AG, Aprather-Weg 18a, D-42115 Wuppertal

(2) Klinik für Nephrologie, Universitätsklinikum Essen, Hufelandstr. 55, D-45122 Essen

Initially the 12,5 kD secreted protein resistin has been identified as an adipocyte-derived cytokine with a functional putative role in regulation of insulin resistance and inflammatory processes. Recent findings suggest its pathophysiological role in vascular cells affecting endothelial function and activation of vascular smooth muscle cells (VSMC) for neointimal thickening and atherosclerotic processes. As a consequence, endothelial dysfunction and constrained blood flow may affect end organ functions of heart and kidney. It is reported that resistin blood levels are increased in patients with chronic kidney disease (CKD).
In the context of the BMBF/ NGFN-Transfer project "New Tools for the prevention of cardiovascular disease in chronic kidney disease - NTCVD" we analysed resistin plasma levels and different biomarkers for tissue injury response, endothelial dysfunction and inflammation in blood samples from 120 patients with CKD (K/DOQI stages 3-5 including hemodialysis patients) and 50 control subjects without CKD (estimated glomerular filtration rate, eGFR above 60 ml/min and no functional or structural renal abnormalities).
Resistin is highly correlated with loss of renal function (by eGFR and albuminuria), and resistin levels correspond consistently with CKD staging.
Noteworthy, plasma level of tissue injury response markers and markers of endothelial dysfunction like lipocalin-2 (NGAL), osteopontin, H-FABP, ADMA, angiopoietin-2, FGF-23 correlate significantly with resistin levels. On the contrary, plasma markers of inflammation like MCP-1, calprotectin, myeloperoxidase, and C-reactive protein (CRP) fail to correlate with resistin concentrations.
This observation supports the postulated mechanism of resistin affecting vascular functions in CKD without apparent involvement of inflammatory disease mediators. In this regard, blocking of resistin action may provide a new target for end-organ protection in chronic-degenerative diseases like CKD.

In patients with severe chronic kidney disease carotid intima-media-thickness and aortic pulse wave velocity are correlated with serum magnesium concentrations

Presenting Author: J. Jankowski
J. Jankowski (1), S. Salem (1), A. Kretschmer (2), T. Krahn (2), V. Jankowski (1), M. Volsek (3), A. Kribben (3), H. Bruck (3)

(1) Medizinische Klinik IV, Charité Universitätsmedizin Berlin, Garystr. 5, D-14195 Berlin

(2) Bayer HealthCare AG, Aprather-Weg 18a, D-42115 Wuppertal

(3) Klinik für Nephrologie, Universitätsklinikum Essen, Hufelandstr. 55, D-45122 Essen

In patients with chronic kidney disease (CKD) vascular calcification is associated with arteriosclerosis, cardiovascular events and mortality. Observational studies suggest that higher serum magnesium (Mg) concentrations in dialysis patients may improve survival and may slow the progression of vascular calcification.
In the context of the BMBF/ NGFN-Transfer project "New Tools for the prevention of cardiovascular disease in chronic kidney disease - NTCVD" we correlated Mg serum concentrations in 36 patients with severe CKD (K/DOQI stage 5, eGFR <15 mL/min or depending on dialysis) and n=61 control subjects without CKD (eGFR >60 mL/min and no structural or functional renal abnormalities) with carotid intima-media-thickness (IMT) and aortic pulse wave velocity (PWV) as surrogate parameters for arteriosclerosis and arterial stiffening.
We classified subjects according to Mg serum concentrations in two groups with low and high Mg serum concentration range (low Mg: 0.62 to 0.89 mmol/l and high Mg: 0.90 to 1.32 mmol/l). In CKD patients magnesium serum concentration correlated with IMT of the right and left carotid artery (IMTleft: 0.97 ± 0.07 vs. 0.78 ± 0.05 mm; IMTright: 0.93 ± 0.08 vs. 0.74 ± 0.04 mm (low Mg n=17 vs. high Mg n=19). In CKD patients we detected a significant lower PWV with higher Mg serum concentration (PWV: 11.7 ± 0.6 vs. 9.6 ± 0.8 m/s (low Mg n=19 vs. high Mg n=17).
In patients with severe CKD low Mg serum concentrations were associated with higher values of IMT and PWV indicating a higher arteriosclerotic burden.
Elevated Mg serum concentrations in CKD patients may counteract vascular calcifications and may result in a lower risk for cardiovascular events and mortality. Therefore, manesium supplementation may be a new option in the treatment and prevention of vascular calcification. However, additional, prospective and interventional studies confirming these findings in clinical settings will have to be performed.

European Sequencing and Genotyping Infrastructure – ESGI

Presenting Author: Sascha Sauer
Sascha Sauer (1), Hans Lehrach (1), Andre Franke (2), Richard Durbin (3), Harold Swerdlow (3), Paul Flicek (4), Jörg Hager (5), Anne Cambon-Thomsen (6), Ivo Gut (7), Xavier Estivill (8), Ann-Christine Syvänen (9), Kurt Zatloukal (10), Birgit Fuchs (11)

1) Max-Planck Institute for Molecular Genetics, (2) University of Kiel, (3) Wellcome Trust Sanger Institute, (4) European Bioinformatics Institute, (5) Centre National de Génotypage, (6) INSERM, (7) Centro Nacional de Análisis Genómico, (8) Centre de Regulació Genòmica, (9) University of Uppsala, (10) Medical University Graz, (11) Gabo:mi

Over the past years, biomedical research has advanced at an incredible rate – particularly in the area of DNA and RNA sequencing. Scientific infrastructures are important to ensure that researchers with various background can make the most of the vast amounts of data being generated in an ambitious genetics or genomics study.
Therefore, the European Sequencing and Genotyping Infrastructure (ESGI), coordinated by the Max-Planck-Institute for Molecular Genetics, pools the efforts of leading European genomics and bioinformatics facilities to provide the larger scientific community with latest genomics technologies and data analysis tools. The main objective of ESGI is to give European researchers direct access to state-of-the-art sequencing and genotyping systems and provide bioinformatics support.
ESGI can deal with a number of diverse projects from external scientists but is in particular interested in; (i) pursuing new ideas and functional genomics projects with a highly innovative and ground-breaking character; (ii) large-scale European population genetics projects.
ESGI opens several calls for proposals to invite external scientists to apply for funding of a study. Accepted projects will be funded by ESGI to cover full costs of consumables and ESGI personnel supporting the project of the external scientists. ESGI funding also includes funding of travel, lodging and subsistence costs of external scientists at an ESGI facility.
To give the researchers in Germany a more precise idea on the infrastructure concept and the possibilities to interact with ESGI, platforms and access modalities for external researchers will be presented in more detail at the NGFN meeting.

Addendum:
1. More information can be found here: http://www.esgi-infrastructure.eu/
2. The next call for proposals for transnational access projects of external scientists is planned for December 2011/January 2012. Please do not miss this opportunity!

Aminoglycoside-mediated Suppression of Obesity Associated Stop Mutations in the Leptin Receptor Gene

Presenting Author: Florian Bolze
Florian Bolze, Sabine Mocek, Martin Klingenspor

Technische Universität München, Molecular Nutritional Medicine, Else Kröner-Fresenius Center and ZIEL-Research Center for Nutrition and Food Science, Gregor-Mendel-Straße 2, D-85350 Freising, Germany

Several inherited diseases are caused by nonsense mutations leading to the formation of truncated proteins. Aminoglycosides such as gentamicin and G418 have the ability to suppress stop mutations during translation thus resulting in a restoration of protein expression and activity. It is hypothesized that aminoglycosides bind to the ribosome and lower the accuracy of codon-anticodon interaction thus allowing the incorporation of a random amino acid at the mutated position. So far no attention has been directed to obesity associated stop mutations as targets for nonsense suppression. Herein we focus on the characterization of stop mutations in the leptin receptor (LEPR) gene: LEPRW31X was identified in obese human subjects; LeprY333X and LeprY763X were detected in a chemically-induced ENU db333/db333 mouse mutant and in the Koletsky rat re-spectively.
In a cell culture based system the three stop mutated Lepr alleles showed a total loss-of-function phenotype characterized by disrupted leptin-induced signalling. Incubation of the cell cultures with gentamicin and G418 reactivated leptin sensitivity of the Lepr variants with different efficiencies most likely due to the different types of premature stop codons: The highest suppression susceptibility was observed for LeprY763X (TAG) followed by LeprW31X (TGA) and LeprY333X (TAA).
Further experiments will help to establish nonsense suppression therapy for obesity and other diseases caused by stop mutations in genes expressed in the brain.

This work was supported by NGFNplus to Martin Klingenspor (01GS0822).

Aberrant neuronal processing of negative facial expressions (fMRI)in the fusiform gyrus of alcohol dependent patients

Presenting Author: Katrin Charlet
Katrin Charlet(1), Karina Naundorf(1), Lina Dornhof(1), Florian Schlagenhauf(1), Anne Beck(1), Jürgen Gallinat(1), Andreas Heinz(1)

(1) Department of Psychiatry and Psychotherapy - Charité Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany

Introduction: Alcohol-dependent patients (AD) experience (more than other addiction patients) deficits in the processing of emotional facial stimuli due to inadequate recognition and incorrect interpretation.

Aim: This study investigated the neural patterns of implicit processing of negative emotional facial cues in AD compared to healthy control subjects (CON).

Methods: In a sample of 66 adult, right-handed participants (33 AD: mean age=44.79 (SD=9.76), 25 males (m) & 8 females (f), mean education years=15.73 (SD=3.85) and 33 CON matched for age, sex and education years) a modified Hariri-Faces task (duration 4:30 min) was conducted at 3T. Data were analysed using SPSS 14.0 and SPM8.

Results: Behavioural data analyses showed no significant differences of the reaction times on emotional cues (faces) and neutral cues (shapes), and the accuracy rates in both conditions in AD compared to CON.
On neuronal level a significant increased BOLD response in the bilateral (L/R) primary visual cortex (BA17), L/R fusiform face area (FFA), L/R amygdale, L/R orbitofrontal cortex (OFC) could be found in both groups during the presentation of faces versus shapes ($p(FWE)<0.05$, $k>10$). Further, an interaction effect of ‘group x condition’ revealed a significant blunted BOLD response in R middle occipital lobe ($p(svc\text{-}FFA)=.03$), L inferior occipital gyrus and R OFC, and increased brain activation in the L subgenual cingulate cortex in the group of AD compared to the group of CON ($p(uncorr)<.001$, $k>10$).

Discussion: These results support findings by Hariri AR et al., Neuroimage (2002), which showed that facial processing is mediated by the amygdale. Interestingly, our results also indicate an altered neuronal activation pattern during the implicit processing of negative emotional faces in the face-specific processing area (FFA), the OFC and affective part of the L cingulate cortex in AD compared to CON.
This study is supported by the Bundesministerium für Bildung und Forschung, 01GS08159.

Detecting outlier peptides in quantitative High-Troughput mass spectrometry

Presenting Author: Florian Erhard
Florian Erhard (1), Ralf Zimmer (1)

(1) Institut für Informatik, Ludwig-Maximilians-Universität München

Quantitative high-throughput mass spectrometry has become an established tool to measure gene expression proteome-wide. The output of such an experiment usually consists of a list of expression ratios (foldchanges) for several thousand proteins. However, there are situations that are far more complex and simple protein foldchanges are not able to account for these complexities: We observed that in several cases individual peptide quantifications show a significantly different foldchange than other peptides from the same protein and that these differences cannot be explained by inprecises measurements.

Such outlier peptides can be the consequence of several technical (misidentifications, misquantifications) or biological (post-translational modifications, differential isoform usage) reasons. In order to unravel those, we developed a method to detect outlier peptides in mass spectrometry data. Our method is able to delineate imprecise measurements from real outlier peptides with high accuracy when the true difference is as small as 0.5 fold on log2 scale.

We applied it on experimental data and investigated the different technical and biological effects that may lead to outlier peptides.
Our method will assist future research to reduce technical errors and bias and also provides a way to find differential isoform usage on proteome level in a high throughput manner.

Distribution of GWAS Disease-Associated SNPs In Epigenetically Modified Regions

Presenting Author: Maxim Barenboim
Maxim Barenboim (1), Thomas Manke (1)

(1) Max Planck Institute of Immunobiology and Epigenetics, Freiburg, Bioinformatics Group

The increasing number of genome-wide association studies (GWAS) has provided plenty of SNPs associated with complex diseases. However, very often positive SNPs and other sequence variations are located in regions such as introns or intergenic space. This makes difficult to categorize SNPs as functional ones and subsequently deduce an underlying molecular mechanism. Thus, these SNPs are often viewed as tag-SNPs in linkage with some other SNPs located in promoter regions, ORFs or splicing sites.

With advances of epigenetics studies it becomes clear that enhancers, modified chromatin and nucleosomes play an important role in regulation of even distantly located genes. This can contribute to development of a complex disease.

By collecting a set of publicly available GWAS SNPs, examining their distribution in DNA surrounding epigenetically modified regions and considering a genomic context we derive an approach that can assist with interpretation of functionality of disease-associated SNPs.

We develop a publicly available tool that can aid with interpretation and a functional assessment of disease-associated SNPs. This tool is based on already established web-tools such as sTRAP which predicts changes in the binding of a transcription factor based on DNA variation, and MicroSNiPer which assists in identifying SNPs affecting microRNA target sites.

Cohesin cooperates with Pluripotency Transcription Factors in the Maintenance of Embryonic Stem Cell Identity.

Presenting Author: Anja Nitzsche
Anja Nitzsche (1), Maciej Paszkowski-Rogacz (1), Filomena Matarese (2), Eva Janssen-Megens (2), Nina Hubner (3), Herbert Schulz (4), Ingrid deVries (1), Li Ding (1), Norbert Huebner (4), Matthias Mann (3), Hendrik G. Stunnenberg (2), Frank Buchholz (1)

(1) Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany

(2) Nijmegen Centre of Molecular Life Sciences, Radboud University, Nijmegen, Netherlands

(3) Max Planck Institute of Biochemistry, Martinsried, Germany

(4) Max-Delbrueck Center of Molecular Medicine, Berlin, Germany

For self-renewal, embryonic stem cells (ESCs) require the expression of specific transcription factors accompanied by a particular chromosome organization to maintain a balance between pluripotency and the capacity for rapid differentiation. However, how transcriptional regulation is linked to chromosome organization in ESCs is not well understood. Here we show that the cohesin component RAD21 exhibits a functional role in maintaining ESC identity through association with the pluripotency transcriptional network. ChIP-seq analyses of RAD21 reveal an ESC specific cohesin binding pattern that is characterized by CTCF independent co-localization of cohesin with pluripotency related transcription factors Oct4, Nanog, Sox2, Esrrb and Klf4. Upon ESC differentiation, most of these binding sites disappear and instead new CTCF independent RAD21 binding sites emerge, which are enriched for binding sites of transcription factors implicated in early differentiation. Furthermore, knock-down of RAD21 causes expression changes that are similar to expression changes after Nanog depletion, demonstrating the functional relevance of the RAD21 - pluripotency transcriptional network association. Finally, we show that Nanog physically interacts with the cohesin or cohesin interacting proteins STAG1 and WAPL further substantiating this association. Based on these findings we propose that a dynamic placement of cohesin by pluripotency transcription factors contributes to a chromosome organization supporting the ESC expression program.

A map of human genome variation from population scale sequencing

Presenting Author: Ralf Sudbrak
R. Sudbrak, M. W. Albrecht, V. Amstislavskiy, T. Borodina, A.N. Davydov, R. Herwig, M. Lienhard, F. Mertes, W. Nietfeld, D. Parkhomchuk, A. Soldatov, M. Sultan, B. Timmermann, H. Lehrach

Max Planck Institute for Molecular Genetics, Berlin, Germany

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 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 2008 by a number of international centres. The aim of the project is to discover genotype and provide accurate haplotype information on all forms of human DNA polymorphism in multiple human populations. During the project pilot phase three studies were conducted to test multiple strategies to produce a catalogue of genetic variants that are present in 1 percent or greater frequency in the different populations chosen for study (European, African and East Asian). The adjacent production phase of the full project combines low coverage whole genome sequencing, array based genotyping, and deep targeted sequencing of all coding regions in 2,500 individuals from five large regions of the world (five population samples of 100 in or with ancestry from each of Europe, East Asia, South Asia and West Africa, and seven populations totalling 500 from the Americas. We increased the low coverage average depth to over 4x per individual. MPIMG successfully finished the phase 1 of the full project by sequencing 54 samples to coverage of 4x. In phase 2 of the full project (total sample size: 1724) 38 additional samples of all 125 samples are/will be analysed. This project will be key for a further understanding of genetic variation and hence have a significant importance for commercial exploitation.

Replicative senescence marker for in vitro expanded mesenchymal stem cells

Presenting Author: Patrick Horn (1,2)
Patrick Horn (1,2), Simone Bork (1,2), Rainer Saffrich (1), Patrick Wuchter (1), Vladimir Benes (3), Dirk Strunk (4), Wolfgang Wagner (5), Anthony D. Ho (1)

(1) Department of Medicine V, University of Heidelberg, Germany

(2) Heidelberg Academy of Sciences and Humanities, Germany

(3) Genomics Core Facility, European Molecular Biology Laboratory, Heidelberg, Germany

(4) Stem Cell Research Unit Graz, Medical University of Graz, Austria

(5) Helmholtz-Institute for Biomedical Engineering, Aachen University Medical School, Germany

Human mesenchymal stromal cells (MSC) raise high hopes for tissue engineering and therapeutic applications. However, due to the lack of specific markers and no uniform standardized methods for cell isolation and culture, standardized MSC preparation is hardly achievable. Reliable quality control of therapeutic MSC products is thus limited. During their expansion prior to application, MSC additionally undergo cellular aging, a process called replicative senescence. This process is characterized by cell enlargement, loss of differentiation potential and growth arrest, which might comprise negative effects for their clinical use.

Our studies revealed consistent alterations in methylation patterns, gene- and miRNA expression upon replicative senescence of MSC. These changes were not restricted to later passages, but were continuously acquired with increasing passages. Furthermore, we have compared gene-expression datasets of different MSC preparations to asses the question, if MSC from different laboratories, isolated and cultured under different conditions, undergo the same gene expression changes upon in vitro culture long-term expansion. A panel of eight specifically up- and down-regulated senescence associated genes could be identified and verified by RT-PCR. Thus, independent of MSC processing methods, these genes provide a practicable approach to assess MSC quality with regard to the state of replicative senescence prior to clinical application.

These findings contribute to a better understanding of the process of replicative senescence. In advance of therapeutic application, the panel of genes we have found offers a feasible approach to assure a higher quality and minimize possible negative side effects of therapeutic MSC.

The GeneCascade - a comprehensive website for disease mutation discovery

Presenting Author: Dominik Seelow
Dominik Seelow (1,2), Jana Marie Schwarz (1,2), Markus Schuelke (1,2)

(1) Charité Universitätsmedizin Berlin, NeuroCure Clinical Research Centre

(2) Charité Universitätsmedizin Berlin, Neuropädiatrie

The GeneCascade is a web-base software suite aimed at the discovery of disease genes and mutations. It consists of 3 tools:
HomozygosityMapper2011 (http://www.homozygositymapper.org) allows the rapid identification of disease-linked regions in humans or animals with an inbreeding background on the basis of SNPs or NGS genotypes. It is based on a model-free algorithm, robust against genotyping errors and numbers of magnitudes faster than conventional linkage analysis. HM detects candidate regions and displays the underlying genotypes graphically. It integrates the candidate gene determination with GeneDistiller (see below). Researchers can at any point decide to share their results with co-workers or to make them publicly accessible on our website.
GeneDistiller2 (http://www.genedistiller.org) is a candidate gene search engine. It displays user-selected gene-specific data such as molecular function or expression for all genes from a genomic region or a candidate gene list. GD highlights interesting features and scores similarities or interactions with known disease genes. GD can sort, filter and even rank genes by their properties. The process remains transparent and researchers can interactively adjust the settings, applying their own background knowledge on the query results. The new release has support for NGS projects and integrates primer design for candidate genes.
The last step in identifying disease mutations is the sequencing of candidate genes or of whole regions or genomes and the evaluation of every single alteration detected. Our tool, MutationTaster (http://www.mutationtaster.org), scores the disease potential of a sequence alteration by various tests for different protein and gene properties. It outperforms similar applications in terms of accuracy (>90% correct predictions) and speed (<0.3s). It also provides an interface to automatically analyse the vast number of alterations found by Next Generation Sequencing and to manage the results.

A high-throughput approach to assess the performance of target enrichment assays

Presenting Author: Peter Frommolt
Peter Frommolt (1,2), Janine Altmüller (1), Ali T. Abdallah (1,2), Susanne Motameny (1), Peter Nürnberg (1,2,3)

(1) Cologne Center for Genomics (CCG)

(2) Cologne Cluster of Excellence on Cellular Stress Responses in Aging-Associated Diseases (CECAD)

(3) Zentrum fuer Molekulare Medizin Koeln (ZMMK)

Target enrichment strategies are widely used to sequence a particular part of an individual genome using next-generation sequencing. Apart from the particular technology being used, the performance of target enrichment assays is highly variable from sample to sample, posing the need for evaluation techniques to review the experiments in a high-throughput fashion. To this end, we developed a novel software package called NGSrich which closes an essential gap in the availability of software packages needed to set up an analysis pipeline for large-scale resequencing studies. We show how we integrated our software into the internal data analysis system of a medium-sized genomics center.
As the technologies of enrichment assays are constantly evolving in a highly dynamic process, the features and performance of the different assays are questioned continuously by the scientific community. To address this question, we show the results of a comparison study on different approaches to exome enrichment. We prepared sequencing libraries of 18 human exomes using 3 different enrichment technologies. After sequencing on an Illumina HiSeq 2000 sequencing instrument, we employed our new software to evaluate and compare the performance of these assays.

Cellular reprogramming of human bone marrow derived mesenchymal stem cells using viral and non-viral approaches

Presenting Author: Matthias Megges
Matthias Megges (1), Alessandro Prigione (1), Sven Geissler (2), Hans Lehrach (1) and James Adjaye (1)

(1) Max Planck Insitut for Molecular Genetics-Berlin, Department Lehrach, Molecular Embryology and Aging Group

(2) Julius Wolff Institut, Campus Virchow-Klinikum-Berlin

The generation of induced pluripotent stem cells (iPSCs) from human mesenchymal stem cells (hMSCs) is a promising approach to alter the short life span in culture and to broaden the restricted differentiation potential of these cells. Currently, the technique to reprogram hMSCs to iPSCs involves expression of the six factors OCT4, SOX2, KLF4, c-Myc, hTERT and SV40LT by retroviruses. However, multiple inserted proviruses decrease genomic stability. This problem could be circumvented when oriP/EBNA1 (Epstein-Barr nuclear antigen-1)-based episomal vectors were used to generate iPSCs from fibroblasts. Therefore this work compares the practicability to derive iPSCs from hMSCs of the same patient by retroviruses using fewer factors and by the non-viral episomal plasmid based method. Doing this, the pos-sibility of enhancing the reprogramming efficiency using different small molecule inhibitors is analyzed. hMSCs derived from a 74 year old patient could be reprogrammed with retroviruses expressing OCT4, SOX2, KLF4 and c-Myc and addition of SB-431542 (TGF-beta receptor inhibitor), PD-325901 (MEK inhibitor) and a P53 inhibitor. A high similarity between hESCs and the derived iPSCs (v-iPSCs) could be confirmed by microarray based expression analysis and embryoid body formation. Reprogramming of hMSCs using episomal plasmids yielded partially reprogrammed iPSC colonies (p-iPSCs) when SB-431542 and PD-325901were used. p-iPSCs were distinct from hESCs and v-iPSCs in terms of morphology and only express a subset of pluripotency markers. However, the cells formed embryoid bodies and spontaneously differentiated into lineages expressing markers of endoderm, ectoderm and mesoderm. Furthermore, p-iPSCs did not form teratomas when injected into immune compromised mice. The MSC- derived p-iPS cell line is an intermediate iPS cell type which bypasses cellular senescence associated with primary hMSCs and meets the in vitro requirements of pluripotency without forming teratomas.

THE ROLE OF USP44 IN HUMAN EMBRYONIC STEM CELLS, RETROVIRAL AND mRNA-DERIVED AMNIOTIC FLUID INDUCED PLURIPOTENT STEM CELLS

Presenting Author: Katharina Wolfrum
Katharina Wolfrum (1), Geertrui Tavernier (2), Joanna Rejman (2) and James Adjaye (1)

(1) Max Planck Institute for Molecular Genetics, Berlin, Germany, Department of Vertebrate Genomics, Molecular Embryology and Aging Group

(2) Ghent University, Ghent, Belgium, Research Group on Nanomedicines

Human amniotic fluid cells (AFCs) have gained increasing appreciation in the biomedical field over the last decade. Due to the presence of fetal stem cells within this heterogenic mixture of cells, which have multipotent capacities, primary human AFCs are believed to be valuable for regenerative therapies in the future. Adding even greater value to AFCs, we and others demonstrated very recently that amniotic fluid cells enable fast and efficient induction of pluripotency. We extensively characterized several retrovirally generated human amniotic fluid-derived induced pluripotent stem cell (AFiPSC) lines. Here, we will present the current status of two of our ongoing AFiPSC-based follow-up projects:
(I) We focus on the optimization of an improved non-viral, mRNA-based reprogramming technique. As our retroviral-derived AFiPSC lines harbour several integration events within their genomes with yet unknown effects on the transcriptome it is our goal to generate integration-free AFiPSC lines. We anticipate that the stem cell-like cells present in bulk primary AFC cultures facilitate the realization of this otherwise rather complex, inefficient mRNA reprogramming approach. This will give us the opportunity to compare the transcriptomes, long-term stability and differentiation potential of our retroviral and mRNA-derived induced pluripotent stem cell (iPSC) lines harbouring identical genetic background.
(II) We aim to knock down the gene encoding the deubiquitinating enzyme USP44 in AFiPSC and human embryonic stem cell (ESC) lines. This enzyme is a critical regulator of the spindle checkpoint during cell cycle. Using an OCT4 ChIP-on-chip approach, we and others identified USP44 as a positively regulated OCT4 target gene in various human pluripotent cell lines. Yet, the exact role of USP44 in the maintenance of self-renewal and pluripotency is unknown. Therefore, utilizing our AFiPSC lines as well as the ESC lines H1 and H9, we will seek to decipher its function.

Derivation of an in vitro model of Nijmegen Breakage Syndrome by somatic reprogramming

Presenting Author: Barbara Mlody
Barbara Mlody (1,2), Ying Wang (1), James Adjaye (1)

(1) Max-Planck Institute for Molecular Genetics, Berlin, Molecular Embryology and Aging Group

(2) Freie Universität Berlin

Nijmegen breakage syndrome (NBS) is an autosomal recessive genetic disorder with mutations in the NBS1 gene. NBS patients display a characteristic facial appearance, microcephaly and a range of symptoms including elevated sensitivity to ionizing radiation, chromosome instability, a high frequency of malignancies, accelerated shortening of telomeres abnormal cell cycle checkpoints, growth retardation and immunodeficiency. The NBS1 encoded protein, NIBRIN, is a component of the MRE11-RAD50-NBS1 (MRN) complex, which is involved in eliciting a response to DNA damage; in particular double-strand breaks (DSB). In addition, NIBRIN has been shown to be an essential modulator in cell cycle checkpoint control, which is an important part of the DNA damage response.
This study aims at generating induced pluripotent stem (iPS) cells from dermal fibroblasts, derived from young donors suffering from NBS. Generation of iPS cells from these patient cell lines will enable us to analyze different distinct cell types after differentiation into hepatocytes, cardiomyocytes or neuronal cells. This in vitro model will aid in the understanding of how the abnormalities affect the reprogramming process and most importantly the mechanisms underlying the disease.
We had several attempts at reprogramming skin fibroblasts derived from seven NBS patients and healthy skin fibroblasts (HFF1) to iPS cells using four retroviruses encoding OCT4, SOX2, KLF4, and c-MYC. But due to the downstream effects of the NBS gene mutation, iPS colonies failed to emerge from more than half of the patient cell lines. We will compare the reprogramming process of NBS patient cell lines with genetically corrected cells by over-expression of non-mutated NBS protein. We also try to track down alternative downstream effects of NBS mutations by global expression profiles of several NBS patient fibroblasts.

Topological analysis and simulation studies of large cellular systems

Presenting Author: Vikash Pandey
Vikash Pandey,Christoph Weirling,Hans Lehrach

Max Planck Institute of Molecular Genetics

To understand the dynamical properties of the cellular system like how complex interaction networks control the cell behaviour one need to resort the formal methods of modelling and simulations of such networks. I want to describe different type of simulation strategy(like ordinary differential equations (ODEs) , Petri nets and flux balanced analysis) to analyze gene expression data with the help of complex biochemical networks. To study different phenotypes with the gene expression data and biochemical networks.

Predicting the disease potential of gene mutations with MutationTaster

Presenting Author: Jana Marie Schwarz
Jana Marie Schwarz (1,2), Christian Rödelsperger (3), Markus Schuelke (1,2), Dominik Seelow (1,2)

(1) Charité – Universitätsmedizin Berlin, NeuroCure Clinical Research Centre

(2) Charité – Universitätsmedizin Berlin, Neuropädiatrie

(3) Charité – Universitätsmedizin Berlin, Institut für Medizinische Genetik

The evaluation of the disease potential of DNA alterations by wet lab means is time and cost intensive. Especially when it comes to Next Generation Sequencing projects and thousands of variations have to be tested for their possible effect, in silico approaches are inevitable.
Here we present MutationTaster, an automatic solution to disease potential prediction. MutationTaster performs various tests both on protein and DNA level which are then scored by a Bayes classifier. In contrast to similar tools, MutationTaster is not limited to single amino acid substitutions. Besides, it has a higher performance and is much faster. We offer an analysis pipeline for raw NGS data as well as tools to use the VCF variants files that are generated by many NGS software suites.
Since its official release in 2009, the protein and genetic data used by MutationTaster was updated several times and a better splicing model was developed. Further harmless polymorphisms and disease mutations were employed to train and optimise the software.
In this presentation, we will illustrate the biological tests included in MutationTaster. We will give examples to demonstrate the intuitive use with single alterations detected by Sanger sequencing. Additionally, we will show how NGS data can be quickly analysed with MutationTaster"s batch query system. Finally, we will highlight why MutationTaster performs better than other tools and which limitations exist.
MutationTaster is freely available at http://www.mutationtaster.org.

Poster Presentation Abstracts

Symposium IV

Genomics of Infection, Inflammation & Environmental Interaction

German Mouse Clinic – New mouse models candidates for allergic diseases using a systemic screening approach

Presenting Author: Juan Antonio Aguilar-Pimentel
Aguilar-Pimentel, J.A.(1,2), Adler, T. (3), Gailus-Durner V.(4), Fuchs H.(4), Schmidt-Weber, C.(2), Hrabé de Angelis, M.(4), Busch, DH.(3), Ollert, M.(1,2)

(1) Technische Universität München, Department of Dermatology and Allergy Biederstein, Munich, Germany;

(2)Center of Allergy and Environment (ZAUM), Technische Universität München and Helmholtz Zentrum München, German Research Center for Environmental Health, Munich, Germany

(3) Technische Universität München, Institute for Medical Microbiology, Immunology, and Hygiene, Munich, Germany.

(4) Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Experimental Genetics, Munich, Germany.

The Allergy screen within the German Mouse Clinic (GMC) is as aim to search for mouse models of allergic diseases and to find new strategies for antiallergic therapy. To identify phenotypic alterations in mice, the use of systemic allergy screening platform able to detect new phenotypes in large groups of animals - both under baseline and/or challenge conditions – using limited amount of biologic sample has been of considerable support.
The well-established challenge screen that includes a model of allergic sensitization and aerosol challenge with different optional allergens, is following by the rapidly quantification of Immunoglobulins (using a Luminex bead-array technology), and cells classification by multi-color flow-cytometry analysis (Eos, PMN, MF, T, B and NK cells) from bronchoalveolar lavage (BAL) and immune phenotyping of lymphocytes and finally a single-step quantification of multiple cytokines from BAL fluid is performed
The outcome of this study has emerged new and interesting mouse lines with particular allergy phenotypes, been able to identified lines with sex dependent immunoglobulin phenotype, distinct T cell activation patterns, and even asymmetry inflammatory response.
In conclusion, we have successfully revealed under a systemic phenotypic allergy screening platform distinct gene functions in a mutant mouse lines that enhance or reduce allergic disease in the murine model. These high-throughput technologies are providing important advances linking new genes that likely will provide vital developments with regard to pathophysiology, diagnosis, and therapy of allergic diseases. (support: BMBF-NGFNplus-01GS0868)

A new animal model for human Listeriosis: in-vivo monitoring of orally infected mice using bioluminescent Listeria monocytogenes

Presenting Author: Silke Bergmann
Silke Bergmann (1), Pip Beard (2), Cormac Gahan (3) Andreas Lengeling (2) and Klaus Schughart (1)

(1) Helmholtz-Centre for Infections Research and University of Veterinary Medicine Hannover, Dept. of Infection Genetics, Inhoffenstraße 7, 38124 Braunschweig

(2) The Roslin Institute an Royal (Dick) School of Veterinary Studies, The University of Edinburgh, Roslin, Midlothian, EH25 9RG

(3) Department of Microbiology, University College Cork, Western Road, Cork, Ireland

The gram-positive bacterium Listeria monocytogenes causes invasive, often fatal, infections in humans and animals. After infection via contaminated food the pathogen is able to cross the intestinal, blood-brain and placental barrier leading to gastroenteritis, meningitis and maternofetal infections which may cause abortion and spontaneous stillbirth.
The primary site of infection is the intestinal epithelium. The bioluminescent Listeria monocytogenes strains EGDe-mur-lux carries two amino acid substitutions in the bacterial invasion protein internalin A (InlAS192NY369S). These alterations increase the affinity of internalin A to murine E-cadherin as compared to wild-type Listeria.

In this study we present data that demonstrate the variations in the virulence of EGDe-lux and EGDe-mur-lux in different orally infected mouse inbred strains (BALB/cJ, C57BL/6J, A/JHsdOla, C3HeB/FeJ). We observed that infection with EGDe-mur-lux resulted in more severe disease symptoms than infection with EGD-lux. Furthermore we found that C57BL/6J mice were more resistant to orally transmitted listeriosis as compared to the other mouse strains. In contrast C3HeB/FeJ and A/JHsdOla mice were more susceptible after oral infection challenge. This was reflected by slower bacterial clearance and reduced survival. In addition the use of bioluminescent bacteria allowed us to study bacterial dissemination in-vivo. Bacterial dissemination to internal organs was analysed and revealed higher bacterial loads after infection with the murinized EGDe-mur-lux strain.

Our experimental system will be used further to study in more detail crossing of the feto-placental barrier in pregnant mice and the blood-brain barrier after oral infection.

Dense Genotyping of Candidate Gene Loci Identifies Variants Associated With oxidized LDL Serum Levels

Presenting Author: Thomas Illig
Mahir Karakas(1), Jens Baumert(2), Norman Klopp(3), Barbara Thorand(2), Christa Meisinger(2), Wolfgang Rottbauer(1), Thomas Illig(3), Wolfgang Koenig(1)

1University of Ulm Medical Center, Internal Medicine II Cardiology, Ulm, Germany

2Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology II, Neuherberg, Germany

3Helmholtz Zentrum München, German Research Center for Environmental Health, Research Unit of Molecular Epidemiology, Neuherberg, Germany

Background: Oxidized low-density lipoprotein (oxLDL) as a marker of oxidative stress has been proposed to play an important role in the development of atherosclerosis. OxLDL consists of a number of heterogeneously modified particles, including apoB, phospholipids, LDL-cholesterol, and unsaturated fatty acids. Serum levels of oxLDL are known to be heritable, but the degree of heritability has not been established yet.

Methods: We used a high-density genotyping array containing single-nucleotide polymorphisms (SNPs) from oxLDL candidate genes selected on known biology of oxLDL metabolism, mouse genetic studies, and human genetic association studies. SNP selection was based on tagging SNPs and included low-frequency nonsynonymous SNPs. 1,332 men and women from a randomly drawn subsample of the baseline examination of the MONICA/KORA Augsburg Cohort Study, conducted between 1984 and 1995, with measurements of oxLDL (Mercodia assay) and genotyping by the 50K IBC Chip comprised the study population. Linear regression analysis with adjustment for age, sex and survey was applied to assess the associations between gene variants and oxLDL levels. Statistical significance was defined as 5.0e-6 accounting for multiple testing.

Results: Eight SNPs showed a statistically significant association with ox-LDL and were located at chromosome 2 in the APOB gene with rs676210 having the strongest association (p value = 4.13e-12). All eight SNPs had minor allele frequencies above 20% showing a substantial gene variation.

Conclusions: In summary, we identified variants in the APOB gene that are associated with levels of oxLDL in the general population. These findings may not only enhance our understanding of oxidative pathways and lipid metabolism and function, but may also pave the way for novel research avenues.

Dense Genotyping of Candidate Gene Loci Identifies Variants Associated With Soluble E-selectin Levels

Presenting Author: Norman Klopp
Mahir Karakas1, Jens Baumert2, Norman Klopp3, Barbara Thorand2, Wolfgang Rottbauer1, Christa Meisinger2, Thomas Illig3, Wolfgang Koenig1

1Department of Internal Medicine II Cardiology, University of Ulm Medical Centre, Ulm, Germany

2Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology II, Neuherberg, Germany

3Helmholtz Zentrum München, German Research Center for Environmental Health, Research Unit of Molecular Epidemiology, Neuherberg, Germany

Background: Elevated soluble (s) E-selectin levels have been associated with various cardiovascular diseases. Recently, genetic variants in the ABO blood group have been related to E-selectin levels in a small cohort of patients with type 1 diabetes. We evaluated whether this association is reproducible in a population-based sample.

Methods: We used a high-density genotyping array containing single-nucleotide polymorphisms (SNPs) from E-selectin candidate genes (50K IBC Chip) selected on known biology of E-selectin metabolism, mouse genetic studies, and human genetic association studies. SNP selection was based on tagging SNPs and included low-frequency nonsynonymous SNPs. 1,508 men and women from a randomly drawn subsample of the baseline examination of the MONICA/KORA Augsburg Cohort Study, conducted between 1984 and 1995, with measurements of sE-selectin and genotyping by the 50K IBC Chip comprised the study population. Linear regression analysis with adjustment for age, sex and survey was applied to assess associations between gene variants and sE-selectin levels. The significance level was defined as 5.0e-6 accounting for multiple testing.

Results: Twelve SNPs, all from the ABO blood group candidate gene (ABO) were significantly associated with levels of E-selectin. The strongest association was observed for rs651007 with a change of E-selectin level per one copy of the minor allele of -18.59 ng/ml ($p=5.79*10^{-56}$). All twelve SNPs had minor allele frequencies above 20% showing a substantial gene variation.

Conclusions: Our findings indicate that the genetic variants at the ABO locus affect sE-selectin levels. These findings may not only enhance our understanding of adhesion molecule biology, but may also provide a focus for several novel research avenues.

Exploring genotype-phenotype relationships in psychiatric disorders using latent semantic analysis

Presenting Author: René Breuer
Rene Breuer (1), Matthias Schubert (2), Josef Frank (1), Manuel Mattheisen (3,4,5), Franziska A. Degenhardt (4,6), Thomas W. Mühleisen (4,6), The Bipolar Genome Study (BiGS) Consortium, Sven Cichon (4,6,7), Markus M. Nöthen (4,6), Thomas G. Schulze(8), Marcella Rietschel (1)

(1) Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health (ZI) Mannheim, University of Heidelberg, Mannheim, Germany, (2) Database Group, Institute for Informatics, Ludwig-Maximilians-University, Munich, Germany, (3) Department of Biostatistics, Harvard School of Public Health, Boston, USA, (4) Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany, (5) Institut of Medical Biometry, Informatics, and Epidemiology, University of Bonn, Bonn, Germany, (6) Institute for Human Genetics, University of Bonn, Bonn, Germany, (7) Institute of Neuroscience and Medicine (INM-1), Research Centre Juelich, Juelich, Germany, (8) Department of Psychiatry and Psychotherapy, University Medical Center, Georg-August-University, Göttingen, Germany

Schizophrenia, bipolar disorder, and major depression are severe, complex psychiatric disorders with a life-time prevalence varying between 0.5-1% for schizophrenia and bipolar disorder, and up to about 15% for major depression. Heritability is estimated in the order of 80-90% for schizophrenia and bipolar disorder, and 33-77% for major depression. Genome-wide association studies (GWAS) for these three disorders have so far identified first genome-wide significant associations with small effects. Recently it was shown that taking into account all tested SNPs they can explain roughly half of the reported heritability. Nevertheless, the question which specific genotype combinations relate to specific phenotype clusters remains a challenging and competitive task which requires further approaches.
Here, we introduce latent semantic analysis, originally applied to text mining (Deerwester et al., 1990), as a novel approach to analyse genome-wide data with respect to various phenotypic traits. The main principle of this approach is the usage of implicit higher-order structures in the association of genetic factors with phenotypic traits. The particular technique used is singular-value decomposition, which decomposes genotypes and phenotypes into a set of meaningful orthogonal factors. The decomposition step is further used to remove noisy implicit structures.
In a train-test-set framework, we explore the ability of this approach to predict the presence of phenotypic traits in patients with bipolar disorder based on genotype data. An adequate accuracy of this approach should lead to genotype-phenotype clusters allowing the identification of genetically more homogeneous subgroups of patients. Latest results from the application to over 3000 patients out of 3 independent bipolar datasets will be presented: the Genetic Association Information Network (GAIN) sample, the Translational Genomics Research Institute (TGEN) sample, and our own German (BoMa) sample.

Impact of MCMV infection on the host miRNA system

Presenting Author: Alexandra Dittmer
Alexandra Dittmer (1), Klaus Förstemann (1)

(1) Gene Center, Ludwig-Maximilian-University, Feodor-Lynen-Str. 25, 81377 Munich, Germany

One goal of viral infection is to reprogram the host cell to optimize viral replication. As part of this process, viral miRNAs may compete for components of the miRNA/siRNA pathway as well as regulate cellular targets. Mouse Cytomegalovirus (MCMV) has been described to generate large numbers of viral miRNAs during lytic infection and was therefore used to analyze the impact of viral miRNAs on the host cell small RNA system as well as to check for sorting of viral small RNAs into specific Ago-proteins.
Deep sequencing analysis of MCMV infected cells showed only app. 13% of all detected miRNAs to be of viral origin in total RNA. All previously described MCMV miRNAs with the exception of miR-m88-1* were present and for the MCMV miR-m01-1 hairpin an additional miRNA, designated as miR-m01-1-3p, was found. Its presence was confirmed by qPCR. Deep sequencing after RISC IP with antibodies specific for either Ago1 or Ago2 showed that all MCMV miRNAs are loaded into both RISC complexes. The ratio of MCMV to mouse miRNAs was lower than that found in total RNA. Viral miRNAs therefore do not appear to either overwhelm the host miRNA system nor are they preferentially loaded.
Only 3 mouse miRNAs showed an altered expression due to MCMV infection. In addition to the already known down-regulation of miR-27a, miR-26a was downregulated as well. Also, an upregulation of miR-7a dependent on viral protein expression could be observed.

Systematic identification of KSHV microRNA targets by a combined proteomics, RIP-Chip and PAR-Clip approach

Presenting Author: Jürgen Haas
Diana Lieber (1), Florian Erhard (2), Georg Malterer (1), Markus Landthaler (3), Susanne M. Bailer (1), Matthias Mann (4), Ralf Zimmer (2), Lars Dölken (1), Jürgen Haas (1,5)

(1) Max-von-Pettenkofer Institute, Ludwig-Maximilians University, Munich

(2) Institute for Bioinformatics, Ludwig-Maximilians University, Munich

(3) Max-Delbrück Zentrum, Berlin

(4) Max-Planck Institute for Biochemistry, Munich

(5) Division of Pathway Medicine, University of Edinburgh

All 12 KSHV miRNAs are encoded in the latency-associated region of the viral genome and are thus expressed during both latent and lytic infection, suggesting a role for KSHV miRNAs in the regulation of latency and reactivation. Due to the complexity of miRNA-target interactions, the investigation of viral miRNA functions requires systematic and state-of-the-art approaches that focus on multiple output levels. In this study, we applied several different experimental approaches to identify targets of KSHV miRNAs in a comprehensive manner. The immunoprecipitation of native RNA-induced silencing complexes (RISC) followed by microarray analysis of co-precipitated target mRNAs (RIP-Chip) lead to the identification of 114 target transcripts of KSHV miRNAs (Dölken et al. 2010 Cell Host and Microbe 7:324), and the additional high-resolution mapping of miRNA binding sites by PhotoActivatable Ribonucleoside-enhanced CrossLinking and ImmunoPrecipitation (PAR-CLIP) is currently in progress. The combination of the RIP-Chip technology with a proteomic approach using stable isotope labeling of amino acids in cell culture (SILAC) in KSHV-infected cells as well as cells ectopically expressing a cluster of 10 intronic KSHV miRNAs enabled us to identify a comprehensive set of high-confidence miRNA targets that is significantly downregulated on the protein level. This set includes cell surface molecules involved in immune recognition and signaling, as well as adhesion molecules whose downregulation might be involved in the phenotypic changes of tumor cells derived from primary effusion lymphomas (PEL). Our study thus presents both comprehensive whole-targetome data that allow to dissect and better understand global miRNA-target interactions and to improve in silico target predictions, as well as functional and mechanistic information on individual viral miRNAs.

Identification and analysis of targets of miRNAs encoded by murine gammaherpesvirus 68

Presenting Author: Martin Strehle
Martin Strehle (1), Olivia Prazeres da Costa (2), and Heiko Adler (1)

(1) Institute of Molecular Immunology, Clinical Cooperation Group Hematopoietic Cell Transplantation, Helmholtz Zentrum München - German Research Center for Environmental Health, Munich, Germany

(2) Institute for Medical Microbiology, Immunology and Hygiene, Technical University Munich, Munich, Germany

The human gammaherpesviruses Kaposi's sarcoma-associated herpesvirus (KSHV) and Epstein-Barr virus (EBV) are associated with a variety of tumors. Infection of mice with the closely related murine gammaherpesvirus 68 (MHV-68) serves as a small animal model to investigate gammaherpesvirus pathogenesis. In this project, we use MHV-68 to study the function of miRNAs encoded by gammaherpesviruses. Recently, by deep sequencing, we identified six new MHV-68 miRNAs (J. Y. Zhu et al. 2010: Identification and analysis of expression of novel microRNAs of murine gammaherpesvirus 68. J. of Virology 84: 10266-10275), which raised the number of known miRNAs encoded by MHV-68 to 15. Now, we aim to identify targets of the MHV-68 miRNAs. For this purpose, three different approaches are undertaken: i) immunoprecipitation of RISC-complexes followed by microarray analysis of the RISC-bound miRNA targets (RIP-Chip); ii) comparison of global gene expression profiles of cells infected with wildtype or with mutant MHV-68 lacking miRNAs; and iii) bioinformatical prediction of miRNA targets using "Targetscan" (www.targetscan.org). Each approach will result in a list of candidate targets. By merging the three lists, we aim to identify the most relevant targets. Finally, selected targets will be further validated. For that purpose, the putative target sequences will be fused to a luciferase reporter gene, and the expression of the reporter gene will be monitored after transfection of the appropriate MHV-68 miRNAs or after infection with MHV-68. Our data will aid to better understand the functions of virally encoded miRNAs during gammaherpesvirus infection.

Exome Data Analysis for a Mendelian Disorder Using a Novel Filtering Tool Reveals the Disease-causing Mutation

Presenting Author: Britt-Sabina Petersen
Britt-Sabina Petersen (1), Björn Stade (1), David Ellinghaus (1), Ingo Thomsen (1), Michael Forster (1), Michael Wittig (1), Georg Hemmrich-Stanisak (1), Abdou ElSharawy (1), Stefan Schreiber (1), Andre Franke (1)

(1) Institute of Clinical Molceular Biology, Christian-Albrechts-University, Kiel, Germany

We have developed a pipeline for the filtering of variants from exome sequencing data for finding disease-relevant ones and demonstrate its functionality using the example of a pedigree affected by a recessive Mendelian disorder.
Four individuals were selected for exome sequencing, three affected and the healthy father of one of the affected. Enrichment was performed using Agilent SureSelect v1 and sequencing was carried out on a SOLiD v4 sequencer. BioScope was used for alignment to the reference and SNPs were identified using two distinct algorithms. Further analyses were performed using our own tool snpActs which annotates the SNPs and displays predictions of various sources for the impact on protein structure and function as well as information from dbSNP, the 1000 Genomes data, HGMD and calculating Grantham scores for a thorough overall picture.
The average on-target coverage was 25x with ~19,000 SNPs identified per exome. Using snpActs, it was possible to find a mutation segregating with the phenotype in the family which is most likely causing the disease. We filtered the data keeping non-synonymous/nonsense and splice-site SNPs not present in dbSNP or any of 200 available exomes of healthy controls (Ng et al. Nature 2009, Li et al. Nat. Genet. 2010) and a maximum frequency of 1% in the 1000 Genomes data. This left us with a single SNP homozygous in all three affected individuals and heterozygous in the unaffected father: a nonsense SNP resulting in truncation of a protein fitting the disease phenotype. Validation by Sanger sequencing has been carried out and functional and genetic follow-up studies are under way.
This example shows the successful application of exome sequencing for finding the cause of a Mendelian disorder. For the main challenge, the variant filtering for finding those involved in disease manifestation, our tool provides an ideal environment by bundling various sources of information in a single step and allowing their collective analysis.

Genome-wide meta-analysis of Psoriatic Arthritis Identifies Novel Susceptibility Locus

Presenting Author: Eva Ellinghaus

Eva Ellinghaus (1), Philip E. Stuart (2), David Ellinghaus (1), Rajan P. Nair (2), Sophie Debrus (3), John V. Raelson (3), Majid Belouchi (3), Trilokraj Tejasvi (2), Yanming Li (4), Anna T. Onken (5), Tonu Esko (6), Andres Metspalu (6), Proton Rahman (7), Dafna D. Gladman (8), Anne M. Bowcock (9), Gerald G. Krueger (10), Sulev Koks (11), Külli Kingo (12), Christian Gieger (13), H. Erich Wichmann (14, 15,16), Ulrich Mrowietz (17), Stephan Weidinger (17), Stefan Schreiber (1), Gonçalo R. Abecasis (4), James T. Elder (2,18), Michael Weichenthal (17) and Andre Franke (1)

(1) Institute of Clinical Molecular Biology, Christian-Albrechts-University, Germany, (2) Department of Dermatology, University of Michigan, USA, (3) Genizon BioSciences, Inc., Canada, (4) Department of Biostatistics, Center for Statistical Genetics, University of Michigan, USA, (5) Department of Dermatology and Allergy, Technische Universität München, Germany, (6) Estonian Genome Center and Center of Translational Genomics, University of Tartu, Estonia, (7) Department of Medicine, Memorial University, Canada, (8) Division of Rheumatology University Toronto, Psoriatic Arthritis Program, Canada, (9) Department of Genetics, Washington University School of Medicine, USA, (10) Department of Dermatology, University of Utah School of Medicine, USA, (11) Department of Physiology, University of Tartu, Estonia, (12) Department of Dermatology and Venerology, University of Tartu, Estonia, (13) Institute of Genetic Epidemiology, Helmholtz Zentrum München, Germany, (14) Institute of Epidemiology I, Helmholtz Zentrum München, Germany, (15) Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-University, Germany, (16) Klinikum Grosshadern, Germany, (17) Department of Dermatology, University Hospital Schleswig-Holstein, Germany, (18) Ann Arbor Veterans Affairs Hospital, USA

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease affecting up to 30% of psoriasis vulgaris (PsV) cases and approximately 0.25% to 1% of the general population. To identify common susceptibility loci, we performed a meta-analysis of three imputed genome-wide association studies (GWAS) on psoriasis, stratified for PsA. Genotype imputation was performed with Beagle v.3.2.1 using HapMap phase 3 reference haplotypes. Only SNPs imputed with high confidence (estimated r2 between imputed and true genotypes >0.8) were used for subsequent logistic regression procedure to test genotyped and imputed SNPs for association. To account for uncertainty in the imputation procedure we used allele dosages from the imputation. A total of 1,166,773 SNPs were analyzed in the discovery set consisting of 532 PsA cases and 3,432 controls from Germany, the United States and Canada. In line with previous studies, we detected the strongest associations with PsA at SNPs in the HLA complex at chromosome 6p21 (rs12212594, $P=5.87\times10^{-38}$). Additionally, we found evidence of association at the previously reported susceptibility loci TNIP1 ($P=4.56\times10^{-10}$) and IL12B ($P=4.85\times10^{-7}$). We followed up two SNPs in 1,821 PsA cases and 6,443 controls comprising six independent replication panels from Germany, Estonia, the United States and Canada. In the combined analysis, a novel genome-wide significant association was detected at chromosome 2 (SNP1, $P=2.03\times10^{-9}$, OR=1.24). The respective polymorphism is known to associate with rheumatoid arthritis, and another SNP near the same gene locus (SNP2) was recently implicated in PsV susceptibility. However, conditional analysis indicated that SNP1, but not SNP2, accounts for the PsA association at that locus. We hypothesize that the implied gene, as a member of the Rel/NF-kB family, is associated with PsA in the context of disease pathways that involve other identified PsA and PsV susceptibility genes including TNIP1, TNFAIP3 and NFkBIA.

HMOX1 gene variants influencing splicing: Association with severe sepsis

Presenting Author: Klaus Huse
Klaus Huse (1), Marcel Kramer (1,2), Christoph Sponholz (2,3), Philip Rosenstiel (4), Michael Bauer (2,3), Matthias Platzer (1)

(1) Genome Analysis, Leibniz Institute for Age Research Fritz Lipmann Institute, Jena

(2) Center for Sepsis Control and Care, Friedrich Schiller University Hospital, Jena

(3) Department of Anaesthesiology and Intensive Care Medicine, Friedrich Schiller University Hospital, Jena

(4) Institute of Clinical Molecular Biology, Christian Albrechts University, Kiel

Heme oxygenases break down heme into equal amounts of carbon monoxide, free iron and biliverdin which is further metabolized to bilirubin, an endogenous inhibitor of inflammatory responses. Regulatory elements in HMOX1, the gene coding for the inducible heme oxygenase 1, have been shown to affect the outcome in various clinical entities, including inflammatory diseases. Here, we tested if a highly polymorphic (GT)n-microsatellite and a single nucleotide polymorphism (SNP rs2071746) in HMOX1 were associated with the outcome of sepsis and whether they affect HMOX1 expression.
430 patients with severe sepsis were genotyped for the SNP and the microsatellite by Sanger sequencing and capillary electrophoresis, respectively. The genotyping results were correlated to clinical and laboratory findings regarding the outcome of patients. RT-PCR and 5'RACE was used to characterize transcript structures. Expression analyses of allelic minigenes were carried out to characterize the impact of SNP and minisatellite alleles on splicing.
Both in the patient cohort and in a control group a trimodal length distribution of the (GT)n repeat was observed. Based on mean-SOFA scores, patients homozygous for the rs2071746 A-allele and with medium length (GT)n-microsatellites (27-33 units) of HMOX1 showed higher 28-day mortality ($p = 0.047$ and $p = 0.033$, respectively) compared to the other genotypes. A novel alternative first HMOX1 exon upstream of the currently annotated exon 1 was identified. According to this revised gene architecture, the (GT)n repeat is an intronic element and was found to influence the generation of alternative splice variants depending on its length.

Transgenic mouse models to study the role of ATG16L1 in intestinal inflammation

Presenting Author: Maren Paulsen
Maren Paulsen (1), Janne Boeck (1), Susanne Billmann-Born (1), Sabine M. Hölter (2), Lillian Garrett (2), Lisa Glasl (2), Annemarie Wolff-Muscate (2), Wolfgang Hans (3), Thure Adler (3,4), Irina Treise (3,4), Jan Rozman (3,5), Monja Willershausen (2), Juan Antonio Aguilar-Pimemtel (3,6), Julia Calzada-Wack (7), Tanja Klein-Rodewald (7), Frauke Neff (7), Dirk H. Busch (4), Irene Esposito (7), Martin Klingenspor (5), Markus Ollert (6), Wolfgang Wurst (3), Valérie Gailus-Durner (3), Helmut Fuchs (3), Martin Hrabe de Angelis (3), Stefan Schreiber (1), and Philip Rosenstiel (1)

(1) Institute of Clinical Molecular Biology, Christian-Albrechts-University, Arnold-Heller-Str. 3, Bldg.5, 24354 Kiel, Germany, (2) Institute of Developmental Genetics, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt, GmbH, Ingoldstädter Landstr. 1, 85764 Neuherberg, Germany, (3) The German Mouse Clinic (GMC), Institut für Experimentelle Genetik, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt, GmbH, Ingoldstädter Landstr. 1, 85764 Neuherberg, Germany, (4) Institute for Medical Microbiology, Immunology, and Hygiene, TUM, Trogerstrasse 30, 81675 München, Germany, (5) Molecular Nutritional Medicine, Else Kröner-Fresenius Center, TUM, Gregor-Mendel-Straße 2, 85350 Freising-Weihenstephan, Germany, (6) Department of Dermatology and Allergy Biederstein, TUM, and Clinical Research Division of Molecular and Clinical Allergotoxicology, TUM, Biedersteiner Str. 29, 80802 München, Germany, (7) Institute of Pathology, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt, GmbH, Ingoldstädter Landstr. 1, 85764 Neuherberg, Germany

In a GWAS study from 2007, we were able to identify an association between allelic variants in the autophagy-regulated gene ATG16L1 and increased susceptibility to Crohn disease (Hampe et al., 2007). ATG16L1 is a component of the autophagy machinery and known for its capacity to regulate cellular homeostasis by maintaining a balance between degradation, synthesis and recycling of cellular proteins. In addition, recent data point to a critical role in autophagic degradation of intracellular bacteria, suggesting a link between ATG16L1 and defense against pathogens, which may be crucial in pathogenesis of intestinal inflammation.
Until now, it is not known how ATG16L1 contributes to the development of intestinal inflammation. Since a full disruption of ATG16L1 in mice is lethal, we investigated heterozygous ATG16L1 KO mice in a systematic first-line phenotyping at the German Mouse Clinic (GMC). The mutant mice displayed significantly decreased locomotor activity. Furthermore flow cytometric analysis of peripheral blood revealed a higher frequency of B cells in the absence of altered Ig levels. Neither did the heterozygous mutation have any effect on energy metabolism nor did analyzed organs and tissues show any pathological alterations.
To gain insights into a possible function of ATG16L1 in the gut, we generated intestinal epithelial cell-specific conditional KO mice (∆IEC). Interestingly, ∆IEC mice were highly susceptible to DSS induced colitis. Furthermore, ATG16L1 deletion leads to reduced autophagy in IEC and to morphological changes in Paneth cells assuming disrupted granula formation and reduced secretory capabilities, replicating findings in hypomorphic mice from other groups (Cadwell et al., 2008). Together, the presented work suggests a crucial role of ATG16L1 for intestinal epithelial immunity and provides a novel tool for dissecting the molecular mechanism of autophagy in different organ systems.

Whole Genome and Transcriptome Sequence of a Crohn Disease Trio

Presenting Author: Matthias Barann
Matthias Barann (1), Ulrich C. Klostermeier (1), Vrunda Sheth (2), David Ellinghaus (1), Tobias Rausch (3), Jan Korbel (3), Michael Nothnagel (4), Michael Krawczak (4), Christian Gilissen (5), Joris Veltman (5), Annette Fritscher-Ravens (6), Michael Forster (1), Björn Stade (1), Stephen McLaughlin (2), Clarence C. Lee (2), Andre Franke (1*), Stefan Schreiber(1,6,*), Philip Rosenstiel(1,*)

(1)Christian-Albrechts-University, Kiel (D), Institute for Clinical Molecular Biology (ICMB), (2) Life Technologies, Beverly, MA 01915 (USA), (3) European Molecular Biology Laboratory (EMBL), Heidelberg (Germany), (4) Christian-Albrechts-University, Kiel (D), Institute of Medical Informatics and Statistics (IMIS), (5) Nijmegen Centre for Molecular Life Sciences (NCMLS), Nijmegen (NL), Department of Human Genetics, (6) Christian-Albrechts-University, Kiel (D), Department of General Internal Medicine,

***These authors contributed equally to the work**

Crohn's Disease (CD) is a chronic inflammatory bowel disease which has been studied thoroughly in the past. As with most complex diseases, however, our understanding of its pathogenesis is still very limited. Studies have shown an increase in CD cases in distant, unrelated populations in the last few years, indicating a global trend. Given the increasing number of CD cases, advancing the knowledge of CD pathology is of pressing importance. It has been reported that all known CD risk loci can only explain about 23.2% of overall genetic heritability. We present an approach to investigate disease relevant genetic variation in relatives' genomes, namely those of a family trio, using next-generation sequencing. The steady drop in cost of whole genome sequencing (WGS), makes WGS more feasible in disease diagnostics. The use of related individuals yields additional power for variation analysis compared to single disease related genomes. The extreme phenotype (early, severe onset) of the diseased child suggests grave genomic differences between it and its healthy parents. We show that the family trio shares a similar, though slightly unusual, genetic background and a comparable distribution of SNPs associated with CD risk with the normal central European population. Despite this, the child is very likely to bare additional, yet unknown genetic mutations which cause CD. In this study we present the most deleterious genetic variations, which have not been associated to CD yet, as well as the most deleterious known CD-risk associated variations detected in the child. Additionally we demonstrate deregulated expression of inflammatory genes in the child compared to the parents by RNA-Seq. To the best of our knowledge we present the first study aiming for the extraction of the full genetic variability in a CD trio and utilizing this data together with genetical genomics analyses by RNAseq as a basis for personalized understanding of the genetic variants causing CD.

A framework to assess technology-specific error signatures in next-generation sequencing, with an application to the 1000 Genomes Project data

Presenting Author: Michael Nothnagel
Michael Nothnagel (1), Alexander Herrmann (2), Andreas Wolf (1), Stefan Schreiber (2), Matthias Platzer (3), Michael Krawczak (1), Jochen Hampe (2)

(1) Institute of Medical Informatics and Statistics, Christian-Albrechts University, Kiel

(2) Department of Internal Medicine I, University Hospital Schleswig-Holstein, Campus Kiel, Kiel

(3) Leibniz Institute for Age Research - Fritz Lipmann Institute, Jena

Next-generation sequencing (NGS) is a key technology in understanding the causes and consequences of human genetic variability. In this context, the validity of NGS-inferred single-nucleotide variants (SNVs) is of paramount importance. We therefore developed a statistical framework to assess the fidelity of three common NGS platforms and to estimate the proportion of false-positives heterozygotes based on read distributions. Application of this framework to aligned DNA sequence data from two completely sequenced HapMap samples as included in the 1000 Genomes Project revealed remarkably different error profiles for the three platforms. Newly identified SNVs showed consistently higher proportions of false positives (3–17%) when compared to confirmed HapMap variants. We show that this increase was not due to differences in flanking sequence features, read coverage or quality, nor was this observation limited to a particular data set or variant calling algorithm. Consensus calling by more than one platform yielded significantly lower error rates (1–4%). This implies that the use of multiple NGS platforms may be more cost-efficient than relying upon a single technology alone, particularly in physically localized sequencing experiments that rely upon small error rates. Our study thus highlights that different NGS platforms suit different practical applications differently well.

First results from the Immunochip project of the International Inflammatory Bowel Disease Genetics Consortium (IIBDGC)

Presenting Author: Tobias Balschun
Tobias Balschun (1), David Ellinghaus (1), International Inflammatory Bowel Disease Genetics Consortium (IIBDGC) (2), Sebastian Zeissig (3), Stefan Schreiber (1,3), Andre Franke (1)

(1) Institute for Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany;

(2) www.ibdgenetics.org; (3) Department for General Internal Medicine, Christian-Albrechts-University, Kiel, Germany.

Introduction: Two recent large-scale GWAS meta-analysis have identified more than 99 risk loci for inflammatory bowel disease (IBD), of which 28 are associated with both subforms of IBD, Crohn’s disease (CD) and ulcerative colitis (UC). The large number of identified risk loci accentuated several key pathways for the pathogenesis of IBD. It is most interesting that several of these pathways were also implicated in the disease-formation of other immune-mediated diseases.
Aims: Identify new risk loci for IBD, identify overlapping disease mechanisms, finemap known risk loci.
Methods: We genotyped more than 14,000 IBD cases and controls in the NGFN genotyping facility in Kiel using a custom-designed Infinium Bead-array from Illumina, the “Immunochip”. This array contains nearly 200,000 single-nucleotide variants (SNVs) inter alia selected from known risk loci of 9 immune-mediated diseases and the previous IBD GWAS meta-analyses. 5,900 of the above-mentioned samples were included in a first case-control analysis which comprised data on more than 11,000 CD cases, more than 9,000 UC cases and more than 12,000 healthy controls.
Results: Several new risk loci have been associated with IBD at the level of genome-wide significance. Some of these loci had been previously described to confer genetic risk for other immune-mediated diseases e.g. STAT4 (asthma, rheumatoid arthritis, systemic lupus erythematosis) or IFNGR2 (asthma, rheumatoid arthritis, sarcoidosis, tuberculosis).
However, other loci were found to be specifically associated with either CD or UC.
Conclusions: We present first results of the analysis of the IIBD-GC Immunochip project. By genotyping huge case-control sets we were able to identify new IBD risk loci previously identified as susceptibility loci for other diseases. We also identified new risk loci for either UC or CD.
Our findings further increase the knowledge on IBD pathogenesis as well as on general pathways in immune-mediated diseases.

A genome-wide association study reveals evidence of association with sarcoidosis at 6p12.1

Presenting Author: Annegret Fischer
Annegret Fischer (1), Michael Nothnagel (2), Karoline Gäde (3), GenPhenReSa Consortium, Philip Rosenstiel (1), Almut Nebel (1), Manfred Schürmann (4), Joachim Müller-Quernheim (5), Sylvia Hofmann (1), Stefan Schreiber (1)

(1) Institute for Clinical Molecular Biology; Christian-Albrechts-University; Kiel, Germany

(2) Institute of Medical Informatics and Statistics; Christian-Albrechts-University; Kiel, Germany

(3) Department of Clinical Medicine; Research Center Borstel; Borstel, Germany

(4) Institute of Human Genetics; University of Lübeck; Lübeck, Germany

(5) Department of Pneumology; University of Freiburg; Freiburg, Germany

Sarcoidosis is a complex systemic inflammatory disease of unknown aetiology that is influenced by a variety of genetic and environmental factors. To identify further susceptibility loci for sarcoidosis, a genome-wide association study was conducted in 381 patients and 392 control individuals based on Affymetrix 100k GeneChip data. The top 25 SNPs were selected for validation in an independent study panel of 1,582 patients and 1,783 controls.
Variant rs10484410 on chromosome 6p12.1 was significantly associated, with a Bonferroni-corrected p value of 0.029 in the validation sample and a nominal p value of 2.64×10^{-4} in the GWAS. Extensive fine mapping of the novel locus narrowed down the signal to a region comprising the genes BAG2, C6orf65, KIAA1586, ZNF451 and RAB23. Verification of the sarcoidosis associated non-synonymous SNP rs1040461 in a further independent case-control sample and quantitative mRNA expression studies point to the RAB23 gene as the most likely risk factor. RAB23 is proposed to be involved in antibacterial defence processes and regulation of the sonic hedgehog signalling pathway.
The identified association of the 6p12.1 locus with sarcoidosis implicates this locus as a further susceptibility factor, and RAB23 as a potential signalling component that may open up new perspectives in the pathophysiology of sarcoidosis.

The European TRIREME project – Dissection of the transcriptional response to DNA damage using an integrated experimental and computational approach

Presenting Author: Hans-Jörg Warnatz
Hans-Jörg Warnatz (1), Emilie Dagand (1), Daniela Balzereit (1), Marc Sultan (1), Aydah Sabah (1), Jeannine Wilde (1), Vyacheslav Amstislavskiy (1), Sharon Rashi-Elkeles (2), Ana Kupershtein (2), Ran Elkon (2), Roye Rozov (3), Ron Shamir (3), Yosef Shiloh (2), Wilfried Nietfeld (1), Hans Lehrach (1) and Marie-Laure Yaspo (1)

(1) Department for Vertebrate Genomics, Max Planck Institute for Molecular Genetics, Berlin, Germany

(2) Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv University, Israel

(3) Blavatnik School of Computer Science, Tel Aviv University, Israel

Genomic stability is essential for cellular homeostasis and prevention of undue cell death or neoplasia. The DNA damage response (DDR) – a complex network of signaling pathways that is vigorously activated by cytotoxic DNA lesions such as double-strand breaks (DSBs) – is central to maintenance of genomic stability. Here, we applied an integrative approach to study gene expression dynamics in human cells treated with a potent DSB inducer, ionizing radiation. DNA microarray analysis, ChIP-seq and advanced computational tools developed in our labs were used to obtain genome-wide delineation of the transcriptional network induced by ionizing radiation (IR) in euploid CAL51 breast cancer cells.
Hundreds of genes responded to ionizing radiation in two waves of both up- and down-regulation. Computational analysis identified p53 and NFkB as major transcription factors (TFs) that modulate these responses. Knock-down of ATM, p53 and the NFkB subunit RelA coupled with ChIP-seq analysis was used to identify the corresponding transcriptional sub-networks and the thousands of genomic target sites to which the TFs are recruited in response to IR. Integration of the expression data and TF-DNA binding profiles allowed us to distinguish between direct and secondary targets of p53 and NFkB. Interestingly, although direct binding of p53 to its target sequences was associated with activation of many of the corresponding genes, the mere binding of RelA to its targets was not sufficient to enhance the transcription of downstream genes. Presently, we are expanding our ChIP-seq data sets by the analysis of the additional factors that were found responsive to treatment of CAL51 cells with ionizing radiation, namely E2F7, CREB1, ATF3, EGR1, JUND, and others. Our analysis reveals the activation of a vast, highly intricate and multi-layered transcriptional network in response to DNA damage.
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Is it possible to quantify and rank the quality of several lists of significant genes found with gene expression profiling by different methods?

Presenting Author: Joachim R. Grün
Joachim R. Grün (1), Andreas Grützkau (1), Biljana Smiljanovic (1), Thomas Häupl (2), Gerd-Rüdiger Burmester (2), Andreas Radbruch (1)

(1) Deutsches Rheumaforschungszentrum (DRFZ) Berlin, (2) Charité CCM Berlin

During gene expression profiling, it is often the question of judging some lists of significant genes (GLs) found with different tools. In the best case, these lists are overlapping only by 70%, often less. Nobody knows which of these different methods comes up with the best list of significant genes. Additionally nearly all tools need some parameters to be entered by the user and dependent of these parameters they give back different GLs. Nobody knows the optimum of the parameters to achieve the optimum GL of the tool. Would it not be very informative if we had a value, which tells us the quality of each of these GLs so that we could rank the quality of them quantitatively?
With Gene List Significance Index (GLSI) we have developed an algorithm with which it is possible to calculate one value for one GL. This value increases with the quality of normalization, with fraction of true positive genes, with fraction of genes with low p values and with fraction of genes with high fold changes. Nevertheless, we showed that in average all normalization methods find the same quality rankings for a given set of GLs. With GLSI it was possible to calculate an empirically score for each gene – High Performance Chip Data Analysis score; HPCDA score – which ranks the genes of one GL in a more objective way than by fold change, p value or any other value.

Selected publications:
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Stittrich A-B et al. The microRNA miR-182 is induced by IL-2 and promotes clonal expansion of activated helper T lymphocytes. Nature Immunology 2010;11/11:1057-1064

The genome of Staphylococcus epidermids O47 - a comparative analysis of a most frequently isolated sequence type (ST 2) S. epidermidis strain

Presenting Author: Stefan Raue
Stefan Raue (1), Ralf Rosenstein (2), Friedrich Goetz (2), Kay Nieselt (1)

(1) University of Tübingen, Faculty of Science, Center for Bioinformatics Tübingen

(2) University of Tübingen, Faculty of Science, Dept. of microbial genetics

The skin colonising coagulase negative Staphylococcus epidermidis causes nocosomial infections and is an important opportunistic and adaptable pathogen. To gain more insight into this species, we sequenced the genome of the biofilm positive, methicillin resistance negative S. epidermidis O47 strain. This strain belongs to the most frequently isolated sequence type 2. In comparison to the RP62A strain, O47 can be transformed, which makes it a preferred strain for molecular studies.

S. epidermidis O47's genome has a single chromosome of about 2.5 million base pairs and no plasmids. Its oriC sequence has the same directionality as S. epidermidis RP62A, S. carnosus, S. haemolyticus, S. saprophyticus and is inverted in comparison to S. aureus and S. epidermidis ATCC 12228. A phylogenetic analysis based on 1200 orthologous genes of all S. epidermidis genomes currently available at GenBank revealed the strain M23864:W2(grey) as the closest relative to O47.

The genome of O47 contains genes for the typical global regulatory systems known in staphylococci. In addition, it contains most of the genes encoding for the typical S. epidermidis virulence factors but not for the typical S. aureus virulence factors with the exception of the putative hemolysin III. O47 has the typical S. epidermidis genetic islands and several mobile genetic elements. To these belongs the staphylococcal cassette chromosome of about 54 kb length and two prophages fO47A and fO47B. On the other hand the genome of O47 has no transposons and the smallest number of IS elements compared to the other known S. epidermidis genomes.

With the sequenced genome of O47 we present the basis for the identification of the genetic and molecular causes of biofilm formation.

Modeling ALB and AFP expression in hepatocyte differentiation and maturation

Presenting Author: Andriani Daskalaki
Andriani Daskalaki (1), Jozefczuk Justyna (1), Hans Lehrach (1), James Adjaye (1), Christoph Wierling (1)

Max Planck Institute for Molecular Genetics, Department of Vertebrate Genomics

Modeling of gene regulatory networks can provide information about the differentiation state of hepatic cells. a-Fetoprotein (AFP) and albumin (ALB) have been identified as model genes to study the regulation of gene expression in the development of hepatic cells. Adult liver shows a reduction in AFP expression, but a gradually increase of ALB expression. Expression of the ALB gene as well as AFP in the liver is controlled by several transcription factors. However, the mechanisms controlling to their regulation require further analysis.
Data related to distinct stages of differentiation from undifferentiated human embryonic stem cells to hepatic endoderm were applied in this analysis. Transcription factors that exert control over transcription at ALB and AFP promoters and associated regulatory networks leading to positive or negative regulation of ALB and AFP have been identified by means of PWM-matching and literature based on these data. We propose a differential equation model including regulatory networks leading to the expression/activation of ALB and AFP has been created with the PyBioS software, a tool for modeling and simulation of cellular processes.
The modeling of transcription factors regulating the expression of ALB and AFP helps us to analyse in depth the processes and associated networks in in vitro derivation of mature hepatocytes.

Global assessment of host cell function in Chlamydia infection using a genome-wide siRNA-based screen

Presenting Author: Erik González
Erik González (1), Marion Rother (1), Nikolaus Machuy (1), André Mäurer (1), Thomas F. Meyer (1)

1: Max-Planck-Institute for Infection Biology, Berlin, Germany

Chlamydia trachomatis is a Gram-negative obligate intracellular bacterial pathogen with a major impact on human health. Despite the prevalence of Chlamydia and their role in human disease, little is known about the mechanisms underlying the infection process, the host pathogen interactions, and the intracellular survival and replication of Chlamydia. Due to the genetic intractability of Chlamydia, the direct functional analysis of suspected virulence factors has been prohibitively difficult, and focuses the study of Chlamydia infection on the role of the host cell.
To investigate these cellular factors, we performed a genome-wide RNAi screen using ~60,000 siRNAs that target ~23,000 human genes (annotated and predicted). Primary hit genes were selected by robust selection criteria and validation of these candidates resulted in the identification of 178 target genes that upon knockdown lead to inhibition of Chlamydia replication. Gene ontology and network analyses of the validated target genes demonstrate enrichment in cellular signaling networks, metabolic and transport processes, e. g. related to nucleotide and lipid metabolism as well as transcriptional control and regulation of the cytoskeleton function.
The identified factors are being analyzed in detail and will help us to better understand interaction between Chlamydia and its host. These results highlight the applicability of our genome-wide RNAi approach for the identification of potential novel targets for antibacterial treatment.

Global analysis of alterations in the host cell epigenetic landscape upon bacterial infection

Presenting Author: Cindrilla Chumduri
Cindrilla Chumduri (1), Sakthimala Jagadeesan(1), Fernando Garcia-Alcalde(1), Thomas F. Meyer(1)

(1) Department of Molecular Biology, Max Planck Institute for Infection Biology, Berlin, Germany

Recent advances implicate that epigenetic mechanisms constitute a heritable phenotype, crucial for controlling cellular development and tissue-specific gene expression patterns. For example, abnormal epigenetic processes can drive cells into altered gene function and malignant cellular transformation. Such changes are reflected by alterations to chromatin on both DNA and DNA-associated histones. Likewise, it has been shown that bacterial and viral pathogens can actively and passively alter host epigenetic processes modifying immunity and inflammatory responses, and contributing to chronic disease. However a deep understanding of this process and its consequences is still missing. The recent development of the so-called Next Generation Sequencing (NGS) technologies constitutes a unique opportunity to investigate host epigenetic changes at an unprecedent rate and precision.

Here we present the findings from a two-fold study:

1)Chlamydiae cause a wide range of human and animal diseases including sexually transmitted diseases and preventable blindness (trachoma). In addition, C. trachomatis (Ctr) is also linked with cervical and ovarian cancer. The potential role of Ctr in inducing heritable epigenetic alterations in the host cell is so far unexplored. Thus, MeDIP-seq (Methyl-DNA immunoprecipitation and sequencing) experiments were performed to investigate the role of Ctr infection in altering host DNA methylation landscape and its influence on transcriptome.

2)Helicobacter pylori infection can result in peptic ulcers and chronic gastritis and is related with the development of gastric cancer. To date, little is known about changes induced by H. pylori infection in the host chromatin states (histone modifications) and their impact on transcriptome. Thus, we performed ChIP-seq (chromatin immunoprecipitation and sequencing) experiments in order to isolate and sequence the DNA associated to H3K4me3 and H3K27me3 in H. pylori-infected gastric epithelial cells.

Poster Presentation Abstracts

Symposium V

Genomics of Cancer

IKZF1 deletion is an independent predictor of outcome in pediatric acute lymphoblastic leukemia treated according to the ALL-BFM 2000 protocol

Presenting Author: Petra Dörge

Petra Dörge (1), Barbara Meissner (1), Martin Zimmermann (2), Anja Möricke (1), André Schrauder (1), Jochen Harbott (3), Wolf-Dieter Ludwig (4), Rolf Köhler (5), Claus R. Bartram (5), Martin Schrappe(1), Martin Stanulla (1), and Gunnar Cario (1)

(1) Department of Pediatrics, University Medical Centre Schleswig-Holstein,Kiel,Germany

(2) Department of Pediatric Hematology and Oncology, Hannover Medical School,Hannover,Germany

(3) Department of Pediatric Hematology and Oncology, University Hospital Giessen and Marburg, Giessen,Germany

(4) Department of Hematology, Oncology and Tumor Immunology, HELIOS-Clinic Berlin-Buch, Berlin, Germany

(5) Department of Human Genetics, University of Heidelberg, Heidelberg, Germany

Within the group of pediatric high-risk acute lymphoblastic leukemia, as defined by minimal residual disease (MRD; $=10^{-3}$ at treatment day 78), a subgroup of patients shows a persistently high tumor load even after additional weeks of very intensive high-risk treatment. These patients are currently incurable and, therefore, the aim of our project is the early identification of these very-high-risk leukemia (VHRL) patients as well as identification and exploration of new treatment targets. In genome-wide screening approaches, copy number evaluation (Affymetrix SNP 6.0 assays) identified a high frequency of deletions (46%) in the IKZF1 gene as a characteristic feature in VHRL patients compared to non-VHRL patients. Subsequently, we screened a cohort of 694 unselected pediatric ALL patients from the ALL-BFM 2000 trial for IKZF1 deletions. Regarding treatment outcome, patients with an IKZF1 deletion had a significantly lower 5-year event-free survival compared to not-deleted patients (EFS, 0.69±0.05 vs. 0.85±0.01; $p < 0.0001$), due to a higher cumulative incidence of relapse (CIR, 0.21±0.04 vs. 0.10±0.01; $p = 0.001$). In multivariate Cox regression analyses, including known prognostic variables, IKZF1 deletion conferred an increased risk of 2.28 for an event when compared to not-deleted patients. IKZF1 deletions were significantly associated with the P2RY8-CRLF2 rearrangement, an additional independent predictor of outcome in ALL-BFM 2000. Adapted multivariate analysis showed, that the IKZF1 deletion retained its prognostic value in patients without the CRLF2 rearrangement. In conclusion, deletion of IKZF1 is an independent predictor of treatment outcome for patients enrolled on the ALL-BFM 2000 protocol and represents a candidate marker. The available copy number data will be investigated for additional targets and complemented by further genome-wide screening approaches in order to build up an integrated VHRL classifier and to discover new treatment options.

Intermediate-risk acute lymphoblastic leukemia (ALL) patients with and without relapse differentially depend on survival signals from microenvironment

Presenting Author: Peter Rhein
Peter Rhein (1), Rita Mitlohner (1), Renate Kirschner-Schwabe (1), Christian Hagemeier (2), Gunnar Cario (3), Martin Stanulla (3), Martin Schrappe (3), Richard Ratei (4), Wolf-Dieter Ludwig (4), Leonid Karawajew (1)

(1) Department of Pediatric Oncology/Hematology, Charité Medical School, Berlin, Germany

(2) Department of General Pediatrics, Charité Medical School, Berlin, Germany

(3) Department of Pediatrics, University Hospital Schleswig-Holstein, Kiel, Germany

(4) Department of Hematology, Oncology and Tumor Immunology, HELIOS Klinikum Berlin-Buch, Berlin, Germany

Risk stratification in childhood ALL has been based on molecular/cytogenetic markers and the response to treatment. These criteria classify about 50% of ALL cases into standard- and high-risk groups. The intermediate-risk (IR) group provides the majority of relapses, but lacks specific prognostic markers which could distinguish between relapsed and relapse-free patients (IR+ and IR-). We established a bank of NOD/SCID ALL xenografts representing IR+ and IR- subgroups and characterized the samples in functional assays. There was no difference in the sensitivity to drugs, however, the rate of spontaneous apoptosis in vitro was significantly higher in IR+ than in IR-. Given that in the presence of stromal cells the cell death level has been similar in both groups, these observations suggest that IR+ is more dependent on survival signals from microenvironment. In the NOD/SCID model, leukemic cells from IR+ engrafted more rapidly than cells from IR-, pointing to a better cooperation between leukemia cells and microenvironment in IR+. In order to identify the underlying molecular pathways, gene expression changes induced in the presence and absence of stroma have been investigated. Of the apoptosis genes, a caspase inhibitior, BIRC3, has been up-regulated significantly higher in IR- than in IR+. The adhesion molecule VCAM1 has been generally up-regulated by the co-incubation with stroma. We further speculated that interaction with microenvironment is a mutual process which also implicates gene expression changes of the stroma. To this end, mouse stromal cells were incubated with ALL samples, purified and investigated using Mouse Gene 1.0 ST arrays. The list of genes whose expression increased, included the chemokine CCL3 known to regulate chemotaxis of lymphocytes. Our data suggest that the cooperation of ALL with microenvironment may provide a promising approach to molecularly discriminate ALL cases with relapse and to identify potential relapse-associated targets.

FUNCTION OF THE MUCIN-LIKE GLYCOPROTEIN PODOPLANIN IN GLIOMA

Presenting Author: Julia Müller
Julia Müller (1), Heike Peterziel (1), Hai-Kun Liu (2), Günther Schütz (2), Jochen Hess (1), Peter Angel(1)

(1) Division of Signal Transduction and Growth Control, DKFZ/ZMBH Alliance, Heidelberg, Germany

(2) Division of Molecular Biology of the Cell I, DKFZ/ZMBH Alliance, Heidelberg, Germany

Previously, employing gene expression profiling of astrocytic glioma samples compared to normal brain we found high expression of the mucin-like glycoprotein Podoplanin (PDPN) predominantly in primary glioblastoma which is associated with poor prognosis (Ernst et al., 2009). Regulation of PDPN expression involved increased PI3 kinase activation mediated by loss of PTEN function, subsequent activation of protein kinase B/AKT and the downstream transcription factor AP-1, and ultimately increased PDPN transcript and protein levels (Peterziel et al., 2011).
We will analyze the regulation and function of Podoplanin in the development and progression of glioma using gain-of-function and loss-of-function approaches in vitro and in vivo by combining work on established human glioma cell lines and analyses of human tumor tissue. Moreover, we have initiated the generation of two neural stem cell specific mouse models of PDPN deletion and overexpression to elucidate the in vivo functions of podoplanin in glioma formation and malignant progression.

Ernst A, Hofmann S, Ahmadi R, Becker N, Korshunov A, Engel F, Hartmann C, Felsberg J, Sabel M, Peterziel H, Durchdewald M, Hess J, Barbus S, Campos B, Starzinski-Powitz A, Unterberg A, Reifenberger G, Lichter P, Herold-Mende C, Radlwimmer B. 2009. Genomic and expression profiling of glioblastoma stem cell-like spheroid cultures identifies novel tumor-relevant genes associated with survival. Clin Cancer Res. 15:6541-6550.
Peterziel, H., Danner, A., Barbus, S., Müller, J., Liu, H.-K., Radlwimmer, B., Pietsch, T., Lichter, P., Schütz, G., Hess, J., Angel, P. Expression of podoplanin in human astrocytic brain tumors is controlled by the PI3K-AKT-AP-1 signaling pathway and promoter methylation. Manuscript in revision.

Molecular pathomechanisms of glioma development in young adults

Presenting Author: Martje Tönjes
Martje Tönjes (1), Andrey Korshunov (2), Ina Kutschera (3), Manfred Schmidt (3), Karin Pfleger (1), Magdalena Schlotter (1), Sebastian Barbus (1), Jörg Felsberg (4), Guido Reifenberger (4), Peter Lichter (1) and Bernhard Radlwimmer (1)

(1) German Cancer Research Center (DKFZ), Heidelberg, Division of Molecular Genetics

(2) German Cancer Research Center (DKFZ), Heidelberg, Clinical Cooperation Unit Neuropathology

(3) National Center for Tumor Diseases (NCT) and German Cancer Research Center (DKFZ), Heidelberg, Department of Translational Oncology

(4) Heinrich-Heine-University, Düsseldorf, Department of Neuropathology

Glioblastoma is the most common and most aggressive type of primary brain tumor in adults. In a previous study we showed that, based on unsupervised analysis of gene expression data, astrocytoma fall into two large subgroups that can be classified based on the mutation status of the isocitrate dehydrogenase 1 (IDH1) gene. IDH1 mutations are present in virtually all anaplastic astrocytomas and secondary glioblastomas, but occur only in a small subset of primary glioblastoma (pGBIV). It currently remains unclear whether these IDH1-mutated pGBIV (pGBIV-IDH1mut) represent a distinct clinical and genetic subgroup. To address this question, we collected tissues of 80 pGBIV from patients younger than 53 years, as IDH1 mutations more frequently occur in younger patients. Pyrosequencing of the IDH1 and IDH2 genes revealed mutations in codon 132 of the IDH1 gene in 30 tumors. The overall survival of pGBIV-IDH1mut patients was significantly longer (34 months) than that of patients with sGBIV or pGBIV-IDH1wt (11 months). Mutation analysis of the TP53 gene revealed diffuse mutation patterns that clearly differed from the more site-specific patterns of other IDH1-mutant astrocytoma such as sGBIV. Unique features of young pGBIV-IDH1mut further included high-level amplifications of glioblastoma-untypical loci, e.g. the podoplanin (PDPN) and MYCN loci. These data indicate that pGBIV with IDH1 mutation indeed constitute a distinct astrocytoma subgroup with regard to patterns of TP53 muitation, chromosome aberrations and patient prognosis. Currently, RNA expression profiles are being generated and compared with data from older adult and from pediatric glioblastoma patients to further deconvolute the effects of genetic aberrations and patient age. These data will help to improve our understanding of glioblastoma pathomechanism and ultimately allow the identification of new disease markers and the development of effective subgroup-specific therapy approaches for high-grade astrocytomas.

Functional characterization of Brd4 as a transcriptional regulator

Presenting Author: Andrea Wunderlich
A.Wunderlich (1), M. Hussong (1), N. Kumer (1), Z. Konthur (1), S. Krobitsch (1), B. Timmermann (3), T. Manke (4), H. Lehrach (1), P. M. Howley (5), M. R. Schweiger (1,6)

(1) Max Planck Institute for molecular Genetics - Berlin, Department Vertebrate Genomics

(2) Max Planck Institute for molecular Genetics - Berlin, Otto-Warburg-Laboratories

(3) Max Planck Institute for molecular Genetics - Berlin, Second Generation Sequencing Center

(4) Max Planck Institute of Immunobiology and Epigenetics - Freiburg, Bioinformatics and Illumina Sequencing

(5) Harvard Medical School - Boston, Department of Pathology

(6) Charité - Berlin, Institute for Medical Genetics

The bromodomain containing protein 4 (Brd4) is involved in the regulation of transcription of human papilloma viruses (HPV) which are the underlying cause of cervical and anal cancers. This HPV transcriptional regulation is due to the interaction of Brd4 and the viral E2 protein which itself binds to the viral genome and thereby tethers the viral genome to mitotic chromosomes. This protein protein interaction also serves as the link to viral persistence through the transduction of the viral genome to the next generation of cells. Similar mechanisms are known in the tumor DNA viruses Epstein-Barr (EBV) and Human Herpes viruses where Brd4 interacts with the viral proteins EBNA1 and LANA1, respectively.
To understand the function of Brd4 in transcriptional regulation and therefore to gain insight into the mechanisms underlying viral cancer pathogenesis we have performed ChIP-Seq and RNA-Seq experiments. We will present this data in combination with co-immunoprecipitations, reporter assays and gene expression analyses to further shed light on the cellular targets of Brd4. This further underscores the role Brd4 plays in cervical, lung and breast cancers.

Genome-wide changes in DNA methylation separate TMPRSS2:ERG fusion negative and fusion positive prostate tumours.

Presenting Author: Stefan T. Boerno
Stefan T. Börno (1,6), Axel Fischer (1), Martin Kerick (1), Maria Fälth (2), Jan-Christoph Brase (2), Ruprecht Kuner (2), Andreas Dahl (3), Uta Marchfelder (1), Christina Grimm (1), Melanie Isau (1,6), Christina Roehr (1,6), Andrea Wunderlich (1,6), Markus Graefen (5), Ronald Simon (4), Guido Sauter (4), Thorsten Schlomm (5), Holger Sültmann (2), Hans Lehrach (1), Michal R. Schweiger (1)

(1) Department of Vertebrate Genomics, Max Planck Institute for Molecular Genetics, Berlin, Germany

(2) Cancer Genome Research, German Cancer Research Center and National Center for Tumour Diseases, Heidelberg, Germany

(3) Biotechnology Center, Technical University Dresden, Dresden,Germany

(4) Institute of Pathology, University Hospital Eppendorf, Hamburg, Germany

(5) Martini Clinic, Prostate Cancer Center, University Hospital Eppendorf, Hamburg, Germany

(6) Department of Biology, Chemistry and Pharmacy, Free University, Berlin, Germany

Prostate cancer is the second most common cancer among men worldwide. Aberrations in the DNA methylation pattern seem to be the leading causes for tumour formation. Here we show genome-wide high throughput sequencing data of DNA methylation in a large cohort of 51 prostate tumour and 53 normal tissues obtained by MeDIP-Seq. Comparative analyses identified more than 147,000 cancer-associated epigenetic alterations occuring during tumourigenesis. Analysing EZH2 polycomb group gene expression we show that EZH2 overexpression might account for differences in DNA methylation patterns between tumour and normal tissues. Furthermore, we show that the methylation patterns in TMPRSS2:ERG fusion negative samples are generally more altered than those in fusion positive tissues leading to the assumption that this outweighs the effects of ERG overexpression and thus lead to cancer initiation as well.

Genome-wide DNA methylation alterations during early steps of intestinal tumor formation in the in the Apcmin/+ mouse model

Presenting Author: Christina Grimm
Christina Grimm (1,5), Lukas Chavez (1), Alexandra Farrall (2), Markus Morkel (2), Mireia Vilardell (1), Bernd Timmermann (3), Michal Ruth Schweiger (1), Matthias Lienhard (1), Jörn Dietrich (1), Julia Böhme (4), Sascha Tierling (4), Marie-Laure Yaspo(1), Jörn Walter(4), Ralf Herwig(1), Bernhard G. Herrmann (2) and Hans Lehrach (1)

(1) Department of Vertebrate Genomics, Max Planck Institute for Molecular Genetics, Berlin

(2) Department of Developmental Genetics, Max Planck Institute for Molecular Genetics, Berlin

(3) Next generation sequencing group, Max Planck Institute for Molecular Genetics, Berlin

(4) Universität des Saarlandes, FR8.3 Biowissenschaften, Genetik/Epigenetik, Saarbrücken

(5) present address: Department of Rheumatology, Charité University Hospital Berlin

Colorectal cancer causes more than 600,000 deaths world wide and mutations in the APC (Adenomatosis Polyposis Coli) gene are common in hereditary and sporadic cases of human colorectal cancer. A widely used mouse model for the early steps of intestinal tumor formation is the Apcmin/+ mouse, carrying a heterozygous muation in the Apc gene. In order to gain insight into the epigenetic and gene expression alterations associated with tumor formation, we generated genome-wide DNA methylation and transcriptome profiles of adenoma and normal mucosa of Apcmin/+ as well as normal mucosa of wild type mice using immunoprecipitation of methylated DNA followed by Illumina sequencing (MeDIP-seq) and RNA-seq. Moreover, to gain insight into the genetic-epigenetic aspects of tumour formation, DNA-methylation and gene expression of Apcmin/+ crosses with B6.PWD chromosome substitution strains showing a reduction in adenoma-load was investigated and compared to the methylation-profiles of the parental adenoma-prone Apcmin/+ mice. We correlated the methylation with the gene expression changes and identified methylation and expression changes occurring already early during tumor development.

Copy number alterations affect the transcriptome, epigenome and mutation patterns of colorectal cancers.

Presenting Author: Michal Ruth Schweiger
Martin Kerick (1,6), Axel Fischer (1,6), Bernd Timmermann (1), Christina Grimm (1), Lukas Chavez (1), Mireia Vilardell (1), Kerstin Neubert (1), Ole Eigenbrod (1), Andreas Dahl (2), Anna Kosiura (1), Stefan Boerno (1), Christian Barmeyer (3), Christina Röhr (1), Andrea Wunderlich (1), Nada Kumer (1), Markus Morkel (1), Alexandra Farrall (1), Christian Viertler (4), Kurt Zatloukal (4), Jörn Walter (5), Melanie Isau (1), Bernhard Herrmann (1), Ralf Herwig (1), Hans Lehrach (1) and Michal-Ruth Schweiger (1)

(1) Max Planck Institute for Molecular Genetics, Berlin

(2) Technical University, Dresden

(3) Charite Berlin

(4) University Hospital Graz

(5) Saarland University

(6) equally contributed

Cancer genomes are known to harbour different combinations of genetic alterations including somatic mutations, copy number variations, structural variations and epigenetic modifications. We used high throughput sequencing strategies to systematically identify these alterations for colorectal cancer cell lines as well as primary tissues from patients. Our re-sequencing experiments are based on whole genome as well as whole exome enrichments followed by high-throughput sequencing. In addition we used RNA-Seq and MeDIP-Seq approaches to characterize the transcriptomes and epigenomes for each sample. Here we investigated the qualities of SNV detections in different sequencing approaches and identify copy number alterations to not only diminish the transcriptome and the methylation patterns but also to affect the SNV distributions. On this basis we demonstrate that CNAs need to be taken into consideration for different biological interpretations of high throughput sequencing data.

Analyses of microRNAs in colorectal cancer and identification of biomarker candidates

Presenting Author: Christina Röhr
Christina Röhr (1), Martin Kerick (1), Karl Kashofer (2), Axel Fischer (1), Stefan Börno (1), Andrea Wunderlich (1), Bernd Timmermann (1), Christina Grimm (1), Thomas Meinel (3), Henry Wirth (4), Hans Binder (4), Kurt Zatloukal (2), Hans Lehrach (1) and Michal-Ruth Schweiger (1,3)

(1) Max Planck Institute for Molecular Genetics, Berlin, Germany;

(2) Medical University of Graz, Austria;

(3) Charité - University Medicine, Berlin, Germany;

(4) IZBI, Leipzig, Germany

Colorectal cancer (CRC) is the third most prevalent malignant neoplasm and a major cause of cancer mortality worldwide. It is known that miRNAs play a critical role in oncogenic signaling pathways, including oncogenesis, progression, invasion, metastasis and angiogenesis. Previous studies of miRNA expression patterns in CRC elucidated a strong association between expression levels of microRNAs and the tumor stage as well as the survival prognosis for cancer patients. To follow up these encouraging results we performed a genome-scale analysis of miRNA expressions using Illumina next-generation sequencing technologies. We sequenced small RNA pools of different colon cancer patients and determined the differences of miRNA expression in matched normal, tumor and metastasis tissues. We identified several alterations in microRNA expression patterns and extended our analyses on single miRNA levels to 330 additional cancer samples. Using this strategy, we were able to identify biomarker candidates for colorectal cancer diagnosis.

Computational analysis of genome-wide methylation with MeDIP-seq

Presenting Author: Lukas Chavez
Lukas Chavez (1), Christina Grimm (1,2), Mireia Vilardell (1), Jörn Dietrich (1), Matthias Lienhard (1), Kerstin Neubert (1), Marcus Albrecht (1), Alexandra Farrall (3), Jörn Walter (4), Kurt Zatlouka (5), Bernd Timmermann (6), Bernhard Herrmann (3), Hans Lehrach (1), Michal Schweiger (1), and Ralf Herwig(1)

(1) Department of Vertebrate Genomics, Max Planck Institute for Molecular Genetics, Berlin

(2) Department of Rheumatology, Charité University Hospital Berlin

(3) Department of Developmental Genetics, Max Planck Institute for Molecular Genetics, Berlin

(4) University of Saarbrücken

(5) Department of Pathology, Medical University of Graz

(6) Next generation sequencing group, Max Planck Institute for Molecular Genetics, Berlin

Advances in the investigation of epigenetic gene control in cancer have demonstrated the fundamental role of epigenetic changes in tumour onset and progression, for example through hypermethylation in promoters of tumour suppressor genes. In the NGFN-plus project "Modifiers of Intestinal Tumor Formation and Progression" we study epigenetic changes in colon cancer with patient samples and mouse models using genome-wide DNA methylation experiments. Methylated DNA immunoprecipitation (MeDIP) depends on the use of an antibody specific for methylated cytosines in order to immunocapture methylated genomic fragments which is combined with next-generation sequencing (MeDIP-seq). We developed and presented the software package MEDIPS, a comprehensive approach for normalization and differential analysis of MeDIP-seq data [1]. Here we first introduce into MeDIP-seq data analysis using MEDIPS. In addition, we present novel results and insights obtained by processing more than 2 billion sequence reads from human and mouse using MEDIPS. For example we have identified thousands of differentially methylated regions (DMRs) by a comparison between colon cancer and matched normal mucosa tissues of 14 different colon cancer patients. Moreover, we have investigated the effect of CNVs present in the genomic backgrounds of different cancer tissues to MeDIP-seq derived methylation signals. Based on Input data, it is possible to estimate events of chromosomal gains or losses. Therefore, MEDIPS was improved in order to incorporate Input-seq data into the analysis. Our results show that in order to reveal the effect of differential methylation on gene expression, identification and correction of copy number alterations are crucial steps towards a more comprehensive understanding of gene regulation.

[1] Chavez, L., et al. Computational analysis of genome-wide DNA methylation during the differentiation of human embryonic stem cells along the endodermal lineage. Genome Res (2010).

The Pacanet iCHIP system - virtual biobanking in NGFN-Plus

Presenting Author: Chris Lawerenz
Chris Lawerenz1, Nathalia Giese2, Anette Heller2, Esther Soyka2, Jens Werner1, Markus Büchler1 Pavel Komardin1, Michael Höhl2, Roland Eils1

1) Theoretical Bioinformatics, DKFZ Heidelberg, INF 580, 69120 Heidelberg

2) European Pancreas Centre, University Clinic Heidelberg, INF 116, 69120 Heidelberg

The creation of a common resources platform is an integral part of any molecular research consortium. Meaningful exploitation of a shareable specimen collection is dependent on the access to comprehensive pathological and clinical annotations.
Pancreatic Cancer Network – PaCaNet – employed an iCHIP-based technology to establish a web-based biobank allowing a central management (Heidelberg) and an access to decentralized clinical specimen (Heidelberg, Bochum, Munich and Marburg).
This platform integrates all workflow steps beginning with patient registration and biosample collection, specimen quality assessment, pathological validation, visual presentation of information and ending with the possibility of an on-line ordering and tracing of the samples, which are distributed to various high-throughput screenings.
Remarkable attention is being paid to confidentiality and security. The introduction of PID (personal identifier)-generator enables the early pseudonymization of patients and permits the transfer and use of data deposited on the dedicated server.
This platform enables the upload and storage of expression profiling, sequencing, imaging and other high screening data in parallel to permanently updated clinical information. This provides a translational research data pool, which is based on verified specimen.

Functional characterization of Cofilin-1 (CFL1) and its proliferative role in pancreatic cancer.

Presenting Author: Sandra Melchisedech
Sandra Melchisedech(1), Tatjana Honstein(1), Ramona Kreider(1), Thomas Gress(1), Malte Buchholz(1)

(1) Clinic for Gastroenterology and Endocrinology, University of Marburg

Within the context of the NGFN PaCaNet consortium, we performed highly parallelized functional analyses of 80 pre-selected pancreatic cancer candidate genes. Overexpression and knockdown experiments in different cell lines were performed via 'reverse transfection' and influences on cell functions examined by fluorescence microscopy and immunocytochemical staining.
Data evaluation showed highly promising effects and led to selection of candidates for further in-depth characterization. Here, we focus on cofilin-1 (CFL1), an actin-modulating protein which binds and depolymerizes filamentous F-actin. CFL1 has a well-studied role in cell migration; however, the results of our parallelized assays indicated that CFL1 also has a previously undocumented role in growth regulation of pancreatic cancer cells. This project thus aimed at examining the functions of CFL1 in pancreatic adenocarcinoma in detail.
Histological staining confirmed a significant overexpression in pancreatic cancer tissues compared to normal pancreatic ducts or chronic pancreatitis. Functional assays were performed after transient overexpression or knockdown of CFL1 in carcinoma cell lines (e.g. PANC-1, S2-007) and non-transformed cells (HEK293). BrdU- and MTT-assays demonstrated a significant reduction of cell proliferation after transient downregulation of CFL1 in 4 different cancer cell lines. Apoptosis was not induced, as shown by Western Blot for Caspase-3 and PARP cleavage. Additionally, knockdown experiments showed a decreased ability for anchorage-independent growth in soft agar assays and a reduced organization of the actin cytoskeleton, as demonstrated by phalloidin staining.
Our results thus demonstrate for the first time a direct growth regulatory function of CFL1 in cancer. Further experiments, including invasion assays to characterize metastatic phenotypes of knockdown and control cells as well as generation of stable knockdown clones for in vivo experiments, are currently in process.

Placenta-specific 8 (Plac8; Onzin) controls proliferation and survival of pancreatic cancer cells

Presenting Author: Tatjana Honstein
Tatjana Honstein(1), Ying Chen(1), Melanie Sauer (1), Harald Schmidt (1), Sandra Melchisedech (1), Ramona Kreider (1), Thomas Gress (1), Malte Buchholz (1)

(1) University of Marburg, Marburg, Clinic for Gastroenterology and Endocrinology

As part of the PaCaNet project within the NGFN program, we have performed highly parallelized functional assays to identify novel genes with central pathophysiological roles in pancreatic cancer. Functional effects of overexpression and knockdown of 80 pre-selected candidate genes in cancer and control cells were examined using reverse transfection microarrays. 19 candidates producing significant and reproducable effects were selected for further in-depth characterization.
The aim of the study reported here was to comprehensively analyze the functional role of one candidate gene, Placenta-specific 8 (Plac8; Onzin). The physiological function of Plac8 is unknown, and it has previously not been implicated in cancer.
Quantitative RealTime PCR analyses confirmed that Plac8 is overexpressed in pancreatic cancer tissues as compared to chronic pancreatitis and healthy pancreas tissue. Likewise, Plac8 is highly expressed in all pancreatic cancer cell lines tested, while it is practically absent in untransformed HEK293 cells. Plac8 gene functions were examined after transient knockdown in four different pancreatic cancer cell lines. MTT and BrdU incorporation assays demonstrated strong inhibition of cancer cell proliferation following downregulation of Plac8. Flow cytometry analyses as well as immunoblot analyses of Cyclins indicated that Plac8 down regulation led to G1/G0 cell cycle arrest. Furthermore, Plac8 knockdown caused massive cell death which was not mediated by canonical apoptosis pathways, as evidenced by Western Blot analyses of Caspase-3 and PARP cleavage.
Taken together, our results thus demonstrate for the first time a central role of the novel gene Plac8 in proliferation and survival of pancreatic cancer cells in vitro. Further work, including experiments to dissect the signalling pathways and regulatory mechanisms involved, as well as in vivo experiments in mouse models of cancer, are currently ongoing.

HNF1A-mediated MIA2 Expression Regulates Metabolism of Pancreatic Cancer and Affects Response to Chemotherapy

Presenting Author: Bo Kong
Bo Kong, Christoph W. Michalski, Weiwei Wu, Chiara Tosolini, Nataliya Valkovska, Mert Erkan, Helmut Friess, Jörg Kleeff

Department of Surgery, Technische Universität München, Munich, Germany

Hepatocyte nuclear factor 1A, HNF1A, a recently discovered pancreatic cancer susceptibility gene, participates in a transcription factor network that regulates development of the pancreas and metabolic processes including carbohydrate and protein metabolism in the adult organ. Here, we show that melanoma inhibitory activity 2, MIA2, is a target of the HNF1A network in pancreatic cancer sustaining the activity of the AKT/mTOR axis to control protein translation; loss of MIA2 in pancreatic cancer cell lines reduced the activity of AKT/mTOR. In line, a common genetic variant of MIA2 (the 617GG and 1833CC haplotype), which potentially affects its cellular localization, was associated with a decreased activity of AKT/mTOR. Pancreatic cancer cells expressing this haplotype endo- or exogenously were highly sensitive to gemcitabine treatment. Because pancreatic cancers that share a similar molecular signature with gemcitabine-sensitive cell lines have recently been shown to be clinically aggressive, we tested pancreatic cancer patients for hetero- or homozygosity of the MIA2 haplotype; here, patients hetero- or homozygous for the haplotype survived significantly shorter than those without it. This implies that pancreatic cancer cells, which are sensitive to non-targeted chemotherapies are actually more aggressive than their chemoresistant counterparts. Thus, our data suggest that HNF1A-mediated MIA2 expression is an important regulatory component of AKT/mTOR signaling in pancreatic cancer. A common genetic variant of MIA2, which significantly influences the metabolism of pancreatic cancer cells, may affect the clinical response to gemcitabine therapy and would thus be a relevant diagnostic target.

Knockdown of kinesin motor protein Kif20a leads to growth inhibition in pancreatic ductal- and neuroendocrine-cancer cells.

Presenting Author: Daniela Stangel
Daniela Stangel(1), Mert Erkan(1), Christoph Michalski(1), Helmut Friess(1), Jörg Kleeff(1)

Klinikum rechts der Isar, TU Munich, Surgery

Introduction: To characterize potential molecular drug targets in pancreatic cancer, Kif20a, a member of the kinesin superfamily involved in trafficking of molecules and organelles was investigated.
Methods: Detection of Kif20a as a druggable candidate was made by combined evaluation of various high-throughput gene analysis panels. In vitro analyses were made in pancreatic ductal adenocarcinoma (PDAC) and neuroendocrine cancer (NEC) cell lines using quantitative realtime-PCR, immunohistochemisty, immumofluorescence, immunoblot analyses and MTT assay. To assess the glycosylation status of Kif20a, Tunicamycin was used as an inhibitor.
Results: Immunohistochemical analysis of paraffin embedded pancreatic tumor samples showed a stronger staining in cancer than in healthy pancreatic tissues. Stronger immunostaining was also observed in several altered acinar cell clusters in chronic pancreatitis. Immunofluorescence analysis of pancreatic ductal- and neuroendocrine cancer cells lines showed nuclear and cytoplasmic localization of Kif20a. mRNA and protein expression of Kif20a was comparable in three PDAC and three NEC cell lines. Knockdown of Kif20a with small interfering RNA molecules has led to 35-40% and 15-30% reduction of proliferation in PDAC and NEC cell lines, respectively. Tunicamycin treatment of PDAC cells showed a decreased level of N-glycosylation of Kif20a.
Conclusion: With an upregulation of more than 10-fold in pancreatic cancer cells, Kif20a appears as a suitable candidate for inhibiting tumor growth in pancreatic cancer.

Kinase-targeted proteomics after Hsp90 inhibition reveal new clients and differences in the response of primary and cancer cells

Presenting Author: Armin Haupt
Armin Haupt (1,5), Gerard Joberty (2,5), Holger Froehlich (2,4), Marcus Bantscheff (2), Henning Stehr (1), Michal R. Schweiger (1), Axel Fischer (1), Martin Kerick (1), Stefan Boerno (1), Andreas Dahl (1), Michael Lappe (1), Hans Lehrach (1), Cayetano Gonzalez (3), Gerard Drewes (2) and Bodo M.H. Lange (1)

(1) Max-Planck Institute for Molecular Genetics, Department of Vertebrate Genomics, Ihnestrasse 73, 14195 Berlin, Germany

(2) Cellzome AG, Meyerhofstrasse 1, 69117 Heidelberg, Germany

(3) Cell Division Group, IRB-Barcelona, PCB, c/Baldiri Reixac 10-12, Barcelona, Spain

(4) present address: International Center for Information Technology, University of Bonn, D-53113 Bonn

(5) these authors contributed equally to this work

The heat shock protein 90 (Hsp90) is required for the stability of many kinases, receptors and mutated oncogenes. Therefore Hsp90 is an attractive target of cancer therapy, because its inhibition causes the simultaneous degradation of these proteins affecting multiple signalling pathways in parallel.
In this study we investigated the effect of Hsp90 inhibitor geldanamycin on the kinome in a human primary fibroblast cell line and three cancer cell lines using isobaric tags (TMT) quantitative mass spectrometry with kinase enrichment (Kinobeads). We validated our results by western blotting. Applying the Kinobeads method we quantified 144 kinases most of which are degraded after Hsp90 inhibition. Down-regulation of many known Hsp90 client proteins underscores the consistency of our data with previous work. We present 44 new potential Hsp90 substrates including kinases of the BMP signalling implicated before in tumour progression. Kinases of MAPK and TGFß signalling routes are more strongly affected in cancer cells. Second generation sequencing identified potentially function-altering missense mutations in 24 identified kinases. We can correlate a subset of these mutations with a differential response in the affected cell line. Structural modelling of candidate client RIPK2 suggests an impact of a mutation on a proposed Hsp90 binding site.
Our work for the first time systematically investigates the differences between primary and cancer cells upon Hsp90 inhibition on the level of regulatory kinases. We propose the now expanded list of Hsp90 clients and pathways identified to react with higher sensitivity to Hsp90 inhibitors and to provide a new opportunities for targeted and combinatorial treatment.

Proteomic and functional characterization of driver mutations in the MAPK signaling pathway – a systems biology approach

Presenting Author: Artur Muradyan
Artur Muradyan (1), Gerard Joberty (2), Anne Kühnel (1), Hans Lehrach (1), Gerard Drewes (2) and Bodo M.H. Lange (1)

(1) Max-Planck Institute for Molecular Genetics, Department of Vertebrate Genomics, Ihnestraße 63-73, 14195 Berlin, Germany

(2) Cellzome AG, Meyerhofstrasse 1, 69117 Heidelberg, Germany

Second generation and classical sequencing approaches have discovered a large number of cancer mutations (http://www.sanger.ac.uk/genetics/CGP/cosmic/). However, the functional and molecular consequence of the majority of these mutations is unclear. The Mutanom consortium (www.mutanom.org) aims to characterize frequently occurring mutations in a systems biology approach. This project combines genomics, proteomics, cellular assays with data collected from model organisms and from the clinic.
Mutations in RAS-ERK signaling pathway often lead to uncontrolled cell growth and tumor expansion. Our initial target list comprises KRAS (wt and 5 mutants), BRAF (wt and 2 mutants) and SRC (wt and 1 mutant). Therefore we generated isogenic cell lines that effectively express inducible wild type or mutated bait protein. Protein complexes are isolated by Tandem Affinity Purification (TAP) and analyzed by quantitative mass spectrometry using isobaric labeling. Comparative analysis of mutants vs. wild type proteins deciphers specific interaction partners. Function of these interactors will be subsequently studied using cell-based approaches (e.g. proliferation, apoptosis, adhesion and migration assays). Additionally, proteome profiling and Kinobeads technology are providing a quantitative readout of the effect of oncogene/tumor suppressor expression for a large set of proteins and kinases, respectively.
This project also tests newly synthesized compounds/inhibitors on BRAFwt, BRAFV600E and BRAFV600K. Application of these compounds on isogenic cells will facilitate understanding of cancer specific signaling events.
Results obtained by proteome analyses, second generation sequencing and mRNA profiling experiments will be integrated in a systems biology model, which is aimed to generate a predictive model of cancer pathways.

IG Mutanom - Systems Biology of Genetic Diseases

Presenting Author: Bodo Lange
B.M.H. Lange (1), A. Brand (2), G. Drewes (3), B. Herrmann (4), G. Joberty (3), U. Korf (5), J. Mollenhauer (6), M. Morkel (4), R. Schäfer (7), M. Schweiger (1), H. Sültmann (5), E. Wanker (8), C. Wierling (1), H. Lehrach (1)

(1) Max-Planck Institute for Molecular Genetics, Vertebrate Genomics, Berlin, Germany

(2) Maastricht University, Maastricht, Netherlands

(3) Cellzome AG, Heidelberg, Germany

(4)Max-Planck Institute for Molecular Genetics, Developmental Genetics, Berlin, Germany, (5)DKFZ, Heidelberg, Germany

(6)Medical Biotechnology Center, University of Southern Denmark, Odense-C, Denmark

(7)Charité-Universitätsmedizin Berlin, Berlin, Germany

(8)Max Delbrück Center for Molecular Medicine, Berlin, Germany

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. Over the last three years our effort has concentrated 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 (COSMIC) and additional mutations have been selected through new generation sequencing approaches. A predictive model has been developed from the quantitative molecular information on signalling pathways obtained from combining functional genomics, proteomics, cellular assays, model organism, structural modelling and clinical data. The developed model and pathway information then be further 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.

Systems Level Analysis and Modeling of Cancer Pathways

Presenting Author: Christoph Wierling
Christoph Wierling, Alexander Kühn, Jian Li, Hendrik Hache, Andriani Daskalaki, and Hans Lehrach

Max Planck Institute for Molecular Genetics, Department Vertebrate Genomics,

Systems Biology Group, Ihnestr. 63 - 73, D-14195 Berlin, Contact: wierling@molgen.mpg.de

Cancer is known to be a complex disease and its therapy has turned out to be difficult. Much information is available on molecules and pathways involved in cancer onset and progression. By processing literature information and pathway databases of twenty different signaling pathways known to be relevant for cancer (like Wnt, Notch, BMP, Fas, Trail, EGF, IGF, Hedgehog, etc.), we have developed a large mathematical model of these pathways. Although the development of large detailed mathematical models is difficult, the benefit one could gain using their predictive power is tremendous. The development of such detailed mathematical models is not only hampered by a limited knowledge about the topology of the cellular reaction network, but also by a highly restricted availability of detailed mathematical descriptions of the individual reaction kinetics along with their respective kinetic parameters. To overcome this bottleneck we introduce an approach, based on a Monte Carlo strategy, in which the kinetic parameters are sampled from appropriate probability distributions and used for multiple simulations in parallel. Results from different forms of the model (e.g., a model that resembles a certain mutation or the treatment by a drug) can be compared with the unperturbed control and used for the prediction of the effect of the perturbation. The established resources, tools, algorithms and models build a foundation for the application of systems biology strategies in medical and pharmaceutical research and, based on data from high-throughput genome, transcriptome, and proteome analysis, it enables the development of a personalized medicine.

High throughput sequence analysis of predisposing and somatically mutated genes in lung cancer for a PREDICTion of chemotherapy resistance

Presenting Author: M. Isau
M. Isau (1,2), A. Fischer (1), M. W. Albrecht (1), K. Neubert (1), R. Yildirimann (1), A.Kosiura (1), U.Marchfelder(1), S.Boerno(1,2), M.Sultan (1), M. Ehremann (3), J. Rolff (3), J. Merk (4), I. Fichtner (3), H. Hülsemann (5), M. Becker (4), R. Kunert (5), H.Sültmann (5), H.Lehrach (1), R. Herwig (1) and M.R. Schweiger (1)

(1) Max Planck Institute for Molecular Genetics, Berlin,Germany

(2)Free University Berlin, Germany

(3)Experimental pharmacology & oncology Berlin-Buch GmbH

(4)Evangelische Lungenklinik Berlin

(5)Unit Cancer Genome Research Heidelberg, Germany

With the development of next generation sequencing technologies it has become feasible to describe the complex genetic networks underlying tumors and thus to identify pathomechanisms of tumor progression and therapy resistance. Hope arises that it will be possible to design chemotherapeutic regimens for each cancer patient individually based on the specific genomic patterns.
Lung cancer is the most frequent cause of cancer-related death worldwide. This is on one hand due to diagnoses at advanced stages and high frequencies of chemotherapeutic resistances. Together with clinicians and specialists in the field of tumor biology and pharmacology we are using 45 primary lung tissue material, xenograft models and cell lines to set up a comprehensive picture of genomic and proteomic alterations underlying lung cancers. Here we will present our data achieved with high throughput sequencing approaches. To avoid the problems in large-scale sequencing projects, which are still relatively cost - and time - intensive for whole genome sequencing, we have used a solution based whole exome as well as a custom designed target enrichment technology followed by massively parallel sequencing with the SOLiD platform and compare genetic information with clinical data such as therapy resistance.

Generation and comparative analysis of interaction networks for cancer relevant proteins

Presenting Author: Patrick Riechers
Sean-Patrick Riechers, Ronny Kalis, Martina Zenkner, Kistin Rau, Susanne Köppen, Dana Rotte, Jenny Russ, Martin Schäfer, and Erich E. Wanker

Max-Delbrueck-Center for Molecular Medicine Berlin-Buch, Proteomics and Molecular Mechanisms of Neurodegenerative Diseases, Robert-Roessle-Str. 10, D-13125 Berlin-Buch

Cancer is the second most frequent cause of death in humans, which is caused by a combination of different mutations in the genome and predominantly results in regulatory and growth abnormalities.
In this study we have screened 25 targets and their corresponding most relevant mutants using an automated high throughput yeast-two-hybrid approach. This includes for example TP53, PTEN, and HRAS. In the screen we detected 7,997 interactions between 1,679 proteins. The interactions were scored and categorized utilizing a bioinformatics scoring system, based on protein and network topology characteristics. Further bioinformatics studies revealed that signaling related proteins are significantly overrepresented in high scoring interactions. 184 interactions were successfully retested with LUMIER and FRET assays. Furthermore, we observed different interaction patterns between wild type and mutant interactions. In silico, we show that between mutant and wild type interactions the cancer relevant GO terms such as proliferation, apoptosis, and metabolism are differentially represented. The same differential GO term distribution was found in gene expression data in two breast cancer cell line sets, differing in the presence or absence of one specific cancer relevant mutation. Network clustering analysis revealed 116 potential protein complexes. Here mutant and wild type interactions are often organized in different clusters. This supports previous observations that cancer mutations trigger regulatory and functional reorganization of cells. In the predicted complexes 36% of the interactions contain disease genes and 61% drug targets.
Finally, we deliver the first yeast two hybrid cancer related mutant / wild-type differential interaction map with high genomic coverage. This network highlights possible new opportunities in cancer treatment.

The structural impact of cancer-associated missense mutations in oncogenes and tumor suppressors

Presenting Author: Seon-Hi Julia Jang
Henning Stehr (1, *), Seon-Hi J Jang (2, 3, *), José M Duarte (4), Christoph Wierling (3), Hans Lehrach (3), Michael Lappe (1) and Bodo MH Lange (3)

(1) Max-Planck Institute for Molecular Genetics, Structural Proteomics / Bioinformatics Group, Otto-Warburg Laboratory, Boltzmannstrasse 12, 14195 Berlin, Germany

(2) Freie Universität Berlin, Department of Biology, Chemistry and Pharmacy, Takustrasse 3, 14195 Berlin, Germany

(3) Max-Planck Institute for Molecular Genetics, Department of Vertebrate Genomics, Ihnestrasse 73, 14195 Berlin, Germany

(4) Paul Scherrer Institut, Biomolecular Research, Biology and Chemistry, 5232 Villigen PSI, Switzerland

(*) These authors contributed equally to this work

Current large-scale cancer sequencing projects have identified large numbers of somatic mutations covering an increasing number of different cancer tissues and patients. However, the characterization of these mutations at the structural and functional level remains a challenge.
We present results from an analysis of the structural impact of frequent missense cancer mutations using an automated method. The analysis focuses on four structural features: solvent accessibility, protein stability, proximity to functional sites and spatial clustering. We show that by breaking the set of mutations into specific subclasses, functionally relevant information is revealed that may be missed otherwise. The structural effects of ~2000 cancer-associated mutations in oncogenes and tumor suppressors are assessed.
We find distinct mutational patterns in the two cancer gene classes reflecting mechanisms of functional activation and inactivation. Furthermore, the results show that the alteration of oncogenic activity is often associated with mutations at ATP or GTP binding sites. We statistically validate the observations and show that the distinct mutational patterns can potentially be used to pre-classify newly identified cancer-associated genes with yet unknown function.

Lysyl oxidase antagonizes RAS oncogene-mediated transformation

Presenting Author: Sha Liu
Sha Liu (1), Minh-Cam Ha-Thi (1), Reinhold Schäfer (1)

(1) Laboratory of Molecular Tumor Pathology, Institute of Pathology, Charité Universitätsmedizin Berlin, Chariteplatz 1, 10117 Berlin

A systematic analysis of transcriptome alterations mediated by oncogenic RAS pathway signaling revealed down-regulation of multiple target genes involved in negative growth regulation and tumor suppression. For example, the expression of lysyl oxidase (LOX), an extracellular matrix enzyme, is consistently repressed in RAS transformed cells of human, mouse and rat origin. The smaller cleavage product of LOX (an 18 KDa propeptide) inhibits NF-kB signaling. We analyzed the consequences of LOX silencing as well as forced expression in normal precursors and RAS-transformed cells. Transient silencing of LOX expression in telomerized, SV40-transformed BJ fibroblasts (BJELB) resulted in morphological transformation and anchorage independent proliferation. Stable LOX knock-down had similar results and enhanced RAS expression and phosphorylation of MEK1/2. A LOX expression vector controlled by the ubiquitin promoter (Ubc) was transfected into BJELR cells, a RAS-transformed derivative of BJELB. LOX-transfectants expressed LOX 16-fold compared to vector-only transfectants. LOX overexpression reversed the transformed morphology of BJELR cells and inhibited proliferation by 30%. We observed a 90% reduction of anchorage independent growth in semi-solid agar medium in BJELR cells and a 50% reduction in HEK293 cells. The p65 protein (RelA), an NF-kB component, was found to be up-regulated after expressing LOX in BJELR cells. In RAS-transformed rat fibroblasts, LOX expression inhibits focus formation and induces cell cycle arrest in G2/M. We conclude that LOX acts as a transformation-suppressing gene in human fibroblasts and embryonic kidney cells. The effects on the intracellular signaling pathway suggest that LOX down-regulation enables robust oncogenic signalling. Conversely, suppression from LOX expression suggested as a possible therapy for metastatic cancer, may be inefficient in case the RAS pathway is activated by genetic alterations, a frequent event in many types of cancer.

Detection of aberrant methylation patterns in glioblastoma

Presenting Author: Sabine Kelkenberg-Schade
Sabine Kelkenberg-Schade (1), Volker Hovestadt (2), Berit Haldemann (1), Peter Lichter (2), Bernd Korn (4), Bernhard Radlwimmer (2), Maren Scharfenberger-Schmeer (3)

(1) DKFZ - Heidelberg, Genomics & Proteomics Core Facilities (W110)

(2) DKFZ -Heidelberg, Molecular Genetics (B060)

(3) Dienstleistungszentrum Ländlicher Raum (DLR) Rheinpfalz - Neustadt an der Weinstraße

(4) Institute of Molecular Biology gGmbH (imb)- Mainz

Malignant glioma is the most frequent and lethal cancer originating in the central nervous system. The most aggressive subtype is glioblastoma multiforme.

Cancer is a consequence of genetic and other alterations of the genome including epimutations. DNA methylation is essential in normal development; abnormalities, particularly in promoter methylation profiles, have been implicated in many pathologies including cancer.

Comprehensive genetic variation studies have greatly benefited from the introduction of the next-generation-sequencing (NGS) platforms. However, this technology is currently not applicable to whole analysis of epigenetic profiles of complex organisms. Therefore it is necessary to focus on individual genomic subsets of interest by reducing the sequence complexity of the sample.

We have established such an approach using microarray-based genomic selection combined with bisulifte treatment for methylation analysis. A genomic DNA library was hybridized to 385K oligonucleotides that had been arrayed and that represented the target DNA regions covering around 2,5 MB of human chromosome 10q. The captured DNA was eluted from the array and then treated with bisulfite prior to high-throughput sequencing. A total of 320 million reads was performed and the resulting data compared to gene expression profiles that had been previously obtained.
In comparison to normal brain tissue, several genes with alterations in methylation pattern of promoter regions were identified.

Our data suggests that subgenomic enrichment and subsequent bisulfite sequencing can be used for an initial screening to detect candidate genes with aberrant methylation pattern in promoter regions.

Oestrogen Signalling and genomics in 3D breast cancer cell cultures

Presenting Author: Nicole Hallung
Nicole Hallung (1), Frauke Henjes (2), Felix Dreher (1), Dorit Arlt (3), Ulrike Korf (2) and Bodo M.H. Lange (1)

(1) Max-Planck Institute for Molecular Genetics, Department of Vertebrate Genomics, Berlin, Germany

(2) German Cancer Research Center, Molecular Genome Analysis, Heidelberg, Germany

(3) German Cancer Research Center, Division of Stem Cells and Cancer, Heidelberg, Germany

As breast cancer is one of the most common cancers in women worldwide, it has been the subject of intensive biochemical and genetic studies, but we are largely missing the relevant molecular information on tumour development and on dynamic protein interactions. In particular, more quantitative approaches are required to gain better understanding of the molecular action of compounds that modulate, for example, the oestrogen pathway and relevant downstream events in mamma cancer on a cellular and organism level.
Here, we are applying a 3D cell culture model as a system for acini formation of the breast epithelial cell line MCF-10A simulating their glandular organization in tissue. This method helps us to approximate the in vivo properties of cells and their growth and signalling behaviour in comparison to normal monolayer cell cultures.
One focus of this project is to analyse different stages of acini formation by mRNA expression profiling as well as Reverse Phase Protein Array (RPPA) to characterize the signalling cascades leading to the formation of mature acini. Dissection of pathway components via siRNA in combination with functional cellular assays will help to identify the molecular signals that are critical to build these 3D structures.
A second focus of this project is to analyse the influence of cancer associated fibroblasts (CAF) on different breast cell lines (e.g. MCF-10A, MCF-7) in the context of ER signalling and relevant chemotherapeutic treatment. Therefore we will characterize the effect of the co-culture of CAF and breast cancer cell line by RPPA and analyse their interaction in 3D cell culture on a proteomics, mRNA expression and cytological level. This will provide information on the impact of the tumour environment on cancer cell signalling and acinar differentiation in vitro.

RNAi synthetic interaction screen identifies a novel role of TP53 in snoRNP biogenesis

Presenting Author: Dragomir Krastev
Dragomir Krastev (1,2), Frank Buchholz (1,2)

(1) University of Technology Dresden, University Hospital and Medical Faculty Carl Gustav Carus, Department of Medical Systems Biology, Fetscherstrasse 74, D-01307 Dresden, Germany

(2) Max Planck Institute of Molecular Cell Biology and Genetics, 01307, Dresden, Germany

The tumor suppressor gene, TP53, is the most frequently mutated gene in human cancers. Understanding its complex genetic interactions is a promising strategy to specifically target cells that have lost p53 functions. We conducted a genetic interaction screen with the genome-scale enzymatically prepared siRNA (esiRNA) library in an isogenic pair of cell lines that differ only in their TP53 status. We compared the effects of depletion of gene function by RNAi over the proliferation of each cell type. A microscopy-based assay with single cell resolution allowed us to identify those genes that are necessary to maintain viability and proliferation with respect to the TP53 status of the cells.
Interestingly, compared to the number of genes necessary for proliferation of TP53 wild type cells, only a limited number of genes showed synthetic “sick” phenotype with TP53 loss-of-function. One of those genes encodes a protein (UNRIP), which is a member of a complex that facilitates small nucleolar RNP assembly (snoRNP). Quantitative proteomics via stable isotope labeling with amino acids in cell culture (SILAC) revealed that another snoRNP assembly chaperone (Nolc1) is present in UNRIP complexes in a TP53-dependant manner. Nolc1 steady state levels are regulated by TP53. In TP53 loss-of-function cells, Nolc1 is down-regulated rendering the snoRNP assembly pathway more susceptible to further insults e.g. UNRIP depletion. Thus, snoRNP assembly is the process at which UNRIP and TP53 functions converge. Our work suggests that interference with two synthetic interaction pathways is a strategy that could be explored to target specific genetic lesions in cancer.

Human endogenous retrovirus HERV-K(HML-10): effect on gene regulation

Presenting Author: Felix Broecker
Felix Broecker (1,2), Roger Horton (1), Hans Lehrach (1,3), Karin Moelling (1,2,4)

(1) Max Planck Institute for Molecular Genetics, Berlin, Germany

(2) University of Zurich, Zurich, Switzerland

(3) Dahlem Centre for Genome Research and Medical Systems Biology, Berlin, Germany

(4) Institute of Advanced Study, Princeton, USA

The human genome harbors ten families of human endogenous retroviruses (HERVs) related to the betaretrovirus Mouse Mammary Tumor Virus (MMTV), designated HERV-K(HML-1 to -10), where HML stands for human MMTV-like. Within this group, HERV-K(HML-2) is the phylogenetically most recent and active family, which has been shown to be implicated in gene regulation, carcinogenesis and the etiology of a number of autoimmune diseases, such as Multiple Sclerosis. However, other HML families, with the exception of HERV-K(HML-3) and HERV-K(HML-5), remain poorly investigated to date, despite their close relatedness to HERV-K(HML-2). Therefore, in this study, we describe in detail the HERV-K(HML-10) family, also known as HERV-K(C4). We found that, as is the case for most other HML families, HERV-K(HML-10) invaded the ancestral genome approximately 30 million years ago and is thus specific for the Old World Monkeys or Catharrhini parvorder. We provide a complete catalog of HERV-K(HML-10) elements in the human genome and found these to be non-randomly distributed among chromosomes and predominantly associated with gene-dense regions. In addition, among all HML families, HERV-K(HML-10) exhibits the highest proportion of intragenic compared to extragenic elements, indicative for purifying selection during evolution, and consequently a functional role. Finally, we provide evidence that numerous members of HERV-K(HML-10) are still transcriptionally active, suggesting a possible impact on gene regulation by antisense transcription in cis, which might have a particular impact during carcinogenesis.

Modeling miRNA Action in EGF-Signaling Pathway

Presenting Author: Jian Li
Jian Li, Hans Lehrach, Christoph Wierling

Max-Planck-Institute for Molecular Genetics

MicroRNAs have gained significant importance due to their widespread occurrence and diverse functions as regulatory molecules that are essential for cell division, growth, development and apoptosis in eukaryotes. The epidermal growth factor (EGF) signaling pathway is one of the best investigated cellular signaling pathways regulating important cellular processes and its deregulation is associated with severe diseases, such as cancer. In the present study, we introduce a model of the EGF signaling pathway integrating validated miRNA-target information according to diverse published scientific papers. The model consists of more than 1100 reactions and contains 241 miRNAs. The model was developed using the PyBioS systems biology software, which enables modeling, visualization, and simulation of complex biological reaction-networks. We applied quantitative simulation strategies to analyze different miRNAs" impact. Furthermore, we investigated the effects of 100 specific miRNA drugs on this signaling pathway. We demonstrate that the consideration of miRNA regulatory-effects in the EGF-signaling pathway can support the development of new therapeutic strategies against cancer.

Cellular stress response as a mechanism conferring resistance to chemotherapeutics

Presenting Author: Christian Kähler
Christian Kähler (1), Jörg Isensee (1), Anja Nowka (1), Annika Pucknat (1), Wilfried Nietfeld (1), Michal Schweiger (1), Hans Lehrach (1), Sylvia Krobitsch (1)

(1) Max Planck Institute For Molecular Genetics, Dept. Vertebrate Genomics, Ihnestraße 63-73, 14195 Berlin, Germany

Antimetabolites are widely used anticancer drugs. However, clinical applications are limited due to drug resistance and the mechanisms conferring resistance to tumors are not completely understood. The uracil analogue 5-fluorouracil (5-FU) and the cytidine nucleoside analogue gemcitabine are used as single agents as well as in combination for cancer treatment. 5-FU inhibits thymidylate synthase interfering with nucleotide synthesis. Both 5-FU and gemcitabine and 5-FU can be misincorporated into DNA leading to DNA damage, or into RNA potentially affecting RNA processing and function.
To identify yeast genes conferring resistance to 5-FU, we performed screens based on a S. cerevisiae deletion library. 54 genes were found to be associated with 5-FU resistance, many of which have human orthologues mutated in cancer. Interestingly, many of the identified genes are implicated in ribosomal function, tRNA modification as well as the transport and processing of mRNAs.
The yeast gene ASC1 is of particular interest as it is the orthologue of human RACK1, a mediator between apoptosis and the formation of stress granules (SG). Under conditions of cellular stress, mRNAs can be stored in these cytoplasmic structures or transferred to processing bodies (PB) for degradation.Treatment of human cells with 5-FU increased PB formation and induced de novo formation of SG. Furthermore, SG formation was increased in cells exposed to stress, accompanied by changes in SG morphology. Treatment with 5-FU metabolites FUrd or FdUrd proved that SG formation depends on RNA metabolic pathways, and uridine co-treatment rescued 5-FU effects. Gemcitabine alone did not induce SG formation but potentiated the effects of 5-FU. We speculate that SG formation might impair apoptotic pathways, thus counteracting cytotoxic drug effects. The results may have implications for the treatment of cancer.

Analysis of Hedgehog/Gli Signalling and Regulatory Networks in Cancer

Presenting Author: Thomas Keßler
Thomas Keßler1, Hendrik Hache1, Elisabeth Maschke-Dutz1, Svetlana Mareva1, Felix Heeger1, Markus Eberl2, Frank Götschel3, Alexandra Kaser2, Fritz Aberger2, Anna-Maria Frischauf2, Ulrike Korf3, Wilfried Nietfeld1, Hans Lehrach1 and Christoph Wierling1

1 Max Planck Institute for Molecular Genetics, Department of Vertebrate Genomics, Ihnestr. 63-73, 14195 Berlin, Germany;

2 University of Salzburg, Department of Molecular Biology, Division Genomics, Heilbrunnerstr. 34, 5020 Salzburg, Austria;

3 German Cancer Research Center (DKFZ), Divison of Molecular Genome Analysis

B050, Im Neuenheimer Feld 580, 69120 Heidelberg, Germany

Several investigations indicate that persistent activation of the Hedgehog (Hh)/GLI signal plays a critical role in the initiation and growth of a number of human malignancies including prostate, breast, brain, skin, and pancreatic cancer. However, the detailed mechanisms of regulation of Hh/GLI target genes and their associated signaling pathways and regulatory networks in cancer formation are still not well understood.
We have performed several global time course gene expression measurements at multiple time points under defined stimuli of EGF and GLI using among others the human HaCaT keratinocyte cell line. Significantly differentially expressed genes are clustered and genes with Early, Mid and Late response are identified within these clusters, including several known direct EGF and GLI targets. We aim to identify potential new downstream targets and to define the underlying gene regulatory network using reverse engineering strategies. Newly identified targets are then integrated to refine our computational model prototype using the PyBioS modeling system and knowledge from literature and pathway databases. This model is used to generate predictions and suggestions of further experimental validation. Model refinement and validation is done in an iterative manner. Our results improve the understanding of the complex molecular network regulated by oncogenic Hh/GLI signaling and will accelerate the search for novel molecular targets that represent an opportunity for therapeutic intervention.

TREAT20 - Tumor REsearch And Treatment: 20 Patient Pilot

Presenting Author: Alexander Kühn
Alexander Kühn1*, Marc Sultan1*, Christoph Wierling1, Thomas Kessler1, Meryem Avci1, Tatiana Borodina1, Dmitri Parkhomchuk1, Vyacheslav Amstislavskiy1, Markus Ralser1, Christian Regenbrecht2, Reinhold Schäfer2, Manfred Dietel2, Peter Schlag3, Iduna Ficht

(1) Max Planck Institute for Molecular Genetics, Ihnestraße 73, D-14195 Berlin, Germany

(2) Charité-Universitätsmedizin, Charitéplatz 1, D-10117 Berlin, Germany

(3) Charité Comprehensive Cancer Center, Invalidenstraße 80, D-10115 Berlin, Germany

(4) EPO GmbH, Robert-Rössle-Straße 10, D-13112 Berlin, Germany

TREAT20 is a translational medicine pilot project addressing the full molecular genetic analyses, systems biology and treatment recommendations for 20 cases of metastatic melanoma. Cancer therapies only work in a limited fraction of patients, calling for an extensive and individual knowledge of the biology of each tumor. High-throughput next generation sequencing (NGS) of both genome and transcriptome of the tumor offers in-depth information on the DNA alterations and gene pathways associated to the tumor biology.
We have generated NGS data for eight patients, diagnosed with either cutaneous or uveal melanoma, for which we are scoring somatic sequenced variants and RNA expression changes. This extensive characterization of the tumor with innovative technologies includes a "virtual patient" computer modelling system that allows the screening of any drug against the patient's tumor including drugs that have not been developed. The results of these analyses will potentially be able to improve the treatment of these patients.

COPY NUMBER VARIATION ANALYSIS IN 134 UNRELATED PATIENTS WITH MUTATION NEGATIVE ADENOMATOUS POLYPOSIS

Presenting Author: Sukanya Horpaopan
Sukanya Horpaopan (1), Stefanie Vogt (1), Isabel Spier (1), Alexander M Zink (1), Kirsten Wöllner (1), Sandra Pasternack (1), Markus Draaken (1,2), Stefan Herms (1,2), Astrid Kaufmann (1), Dietlinde Stienen (1), Siegfried Uhlhaas (1), Elke Holinski-Feder (3,4), Markus M Nöthen (1,2), Per Hoffmann (1,2), Stefan Aretz (1)

(1) Institute of Human Genetics, University of Bonn, Germany

(2) Dept. of Genomics, Life & Brain Center, University of Bonn, Germany

(3) University Hospital of the Ludwig-Maximilians-University, Campus Innenstadt, Munich, Germany

(4) MGZ - Center of Medical Genetics, Munich, Germany

Background: In up to 50% of patients with colorectal adenomatous polyposis no APC and MUTYH mutation can be identified, although a genetic cause is likely. Copy number variants (CNVs) have recently been recognised as important forms of structural variation which also predispose to human diseases. It can be hypothesised that in particular heterozygous microdeletions contribute to the underlying cause in yet unidentified genes responsible for adenomatous polyposis syndromes.
Methods: Genomic DNA from 134 unrelated mutation negative polyposis patients was used for genome-wide SNP genotyping with the HumanOmni1-Quad BeadArray (Illumina). Putative CNVs were identified by the QuantiSNP v2.2 algorithm, filtered according to various criteria by use of the Cartagenia Bench™software, by in-silico-analysis, and by comparison with 531 healthy controls, and validated by qPCR.
Results: 35 unique heterozygous deletion CNVs containing 38 protein coding genes could be validated in 33 patients (25%) but not in healthy controls. 25 genes are partly or completely deleted and 13 genes are deleted only an intronic region. Additionally, 47 unique duplication CNVs from 38 patients (28%) were validated by qPCR. 49 out of the 106 involved genes are partially duplicated which might point to potential loss-of-function effects. All CNVs are present only once in the whole cohort; all except eight patients harbor just one CNV. Candidate adenoma genes include protein kinases, transcription factors, and potential tumor suppressors.
Conclusions: By applying stringent filter criteria, we identified a group of rare deletion and duplication CNVs which might contain predisposing genes for adenoma formation. After prioritization of the included genes according to expression profiles, function, and pathway, present work includes sequencing the coding regions of the most interesting candidates in all patients to look for pathogenic point mutations. The study was supported by the German Cancer Aid.

Company Satellite Sessions

Abstracts

Benefits of 454 Sequencing in Genome Analysis

Presenting Author: Dr. Bernd Timmermann, Head Next Generation Core Facility

Max Planck Institute for Molecular Genetics, Berlin

Roche Diagnostics Deutschland GmbH

The Sequencing Core Facility of the Max Planck Institut for molecular Genetics is using a combination of short and long read platforms. The main advantages of the 454 technology is the long read length (up to 1000 bases with the GS FLX+ system) and a very high accuracy. Out of this reason the MPI-MG is using the GS FLX+ and GS Junior platforms for a broad range of different applications. Especially for diagnostic approaches (amplicon seq, targeted enrichment) the long reads of the 454 technology are quite useful. In the IRON (Interlaboratory RObustness of Next-Generation Sequencing) study we investigated - as an international consortium - the robustness, precision, and reproducibility of 454 amplicon sequencing across 10 laboratories from 8 countries. We demonstrated in this multicenter analysis that amplicon-based deep-sequencing is technically feasible, achieves a high concordance across multiple laboratories, and allows a broad and in-depth molecular characterization of hematological malignancies with high diagnostic sensitivity.

But also for our de novo projects the long 454 reads are irreplaceable. For small genomes (bacteria or yeast) 454 sequencing is the method of choice, but also for larger genomes a low coverage of ~ 6 X as “backbone sequencing” is the normal procedure in our projects.

For all these projects we have now established an automated 454 workflow, including library peparation, emulsion PCR, sequencing and data analysis.

New processes for large scale DNA extractions at Karolinska Institutet Biobank

Presenting Author: Cecilia Agardh
Cecilia Agardh and Gunnel Tybring

Karolinska Institutet Biobank, Stockholm, Sweden

chemagen Biopolymer-Technologie AG

Back ground: Since its start in 2004 the central biobank at Karolinska Institutet has built up competitive expertise and become a state of the art facility supporting medical research. It provides highly qualified sample handling and storage processes, and distributes samples to analytical platforms worldwide. Until now KI Biobank has served > 70 scientific studies with samples from 125 000 sample donors stored in the biobank. A recently strategic funding on a national biobank infrastructure BBMRI.se made it possible to further invest in equipment which has greatly improved our capacity, quality and experience in sample handling, especially for DNA extraction. The project was driven by three major national studies, two within cancer with a target of 200 000 people and LifeGene with a target of 500 000 people in Sweden.
Methods and results: New robotic systems have been implemented for high through put sorting and aliquotation of different sample types into multiple 220 µl fractions. The process for DNA extraction include mixing of EDTA whole blood to ensure a uniform distribution of leucocytes followed by aliquotation of 400 µl blood into a deep well plate for up front DNA extraction. chemagic STAR instruments in combination with a Hamilton Starlet for blood mixing are used for DNA extraction from 400 µl blood. A Trinenan Dropquant UV spectrophotometer is integrated in the system for online quality and quantity check at 260 nm and 260/280 nm respectively. The mean DNA yield in 400 µl blood extracted from 6150 sample donors is 14,5 µg with a mean concentration of 97 ng/µl ± S.D 29 ng/ul.
Conclusion: The newly established large scale DNA extraction process from 400µl has successfully increased the capacity to 4 x 96 samples/instrument. Our next step is to further increase the capacity and to set up a protocol for extraction from 4 ml blood and saliva.

Genome-Wide Detection and Analysis of Germline and Somatic Variations in Tumors

Presenting Author: Stephen E. Lincoln
Krishna Pant, Geoff Nilsen, Srinka Ghosh, and Stephen E. Lincoln

Complete Genomics,
Inc. Mountain View, California USA

Accurate, complete human genome sequences provide a powerful method for identifying variants, both somatic and germline, involved in clinically relevant diseases and phenotypes. We have developed a technology platform and sequencing center capable of cost-effectively sequencing more than 600 human genomes per month at high-depth (minimum 40x, typically much higher). Bioinformatic analysis is performed using our local de novo assembly-based pipeline which detects SNVs, indels, and substitutions in addition to copy number and structural variants. Recent changes to this pipeline improve sensitivity at loci subject to allelic imbalance in the read set, which may be caused by the presence of normal cells within a tumor specimen, by aneuploidy, or by other heterogeneity within a sample. Algorithms have been developed to allow detailed comparison of evidence at each discordant locus within a tumor-normal pair, allowing one to both improve and tune sensitivity/specificity trade-offs in somatic variation detection. To help discriminate causal variant(s) from the millions of other variants in any genome sequenced, we recently generated high-depth complete human genome data on 69 ethnically diverse non-tumor cell lines from the NIGMS and NHGRI (CEPH/Utah, HapMap and 1000 Genomes Project) collections. These data have been released on ftp2.completegenomics.com. Future updates to these data will be made available, including additional tumor and non-tumor reference DNAs. Comparisons against other public data sets on the same sample data, in addition to validation by traditional methods, shows high genotype concordance.

Ion Torrent PGM™ for Clinical Genetics

Presenting Author: Goran Tomicic

Life Technologies Corporation

Illumina Sequencing - Whole genomes to amplicons

Presenting Author: Neil Ward

Illumina

A presentation of the latest developments in Illumina's sequencing portfolio from recent HiSeq chemistry and software improvements with TruSeq V3 and CASAVA 1.8, through to the latest MiSeq benchtop machine and sequencing data.

Alphabetical List of Participants

Surname	First name	Title	Institution	Email
Abdel-Shafy	Hamdy		Faculty of Agriculture and Horticulture, Berlin	hamdyabdelshafy@hotmail.com
Aden	Konrad	Dr.	Universität Kiel	k.aden@ikmb.uni-kiel.de
Adjaye	James	Dr	Max-Planck Institute for Molecular Genetics, Berlin	adjaye@molgen.mpg.de
Adler	Thure	Dr. vet med.	Helmholtz Zentrum München	thure.adler@helmholtz-muenchen.de
Adler	Heiko	Prof. Dr.	Helmholtz Zentrum München	h.adler@helmholtz-muenchen.de
Agardh	Cecilia		Karolinska Institutet Biobank, Stockholm, Sweden	cecilia.agardh@ki.se
Aguilar-Pimentel	Juan Antonio	Dr. rer. nat.	Klinikum rechts der Isar der TU München	aguilar@helmholtz-muenchen.de
Aigner	Bernhard		LMU Munich	b.aigner@gen.vetmed.uni-muenchen.de
Albrecht	Mario		Max Planck Institute for Informatics, Saarbrücken	mario.albrecht@mpi-inf.mpg.de
Amini	Fahim	Dr.	Complete Genomics Inc.	famini@completegenomics.com
Apelt	Federico		Max Planck Institute for Molecular Genetics, Berlin	fede@gmx.net
Aretz	Axel	Dr.	PT-DLR, Bonn	axel.aretz@dlr.de
Aretz	Stefan	PD Dr.	Institute of Human Genetics, Bonn	Stefan.Aretz@uni-bonn.de
Argo	Silke	Dr.	NGFN Management Office	s.argo@dkfz.de
Arif	Beenish		University of Lubeck	plasmagenes11@yahoo.com
Arning	Astrid	Dr	Leibniz Institut für Arterio-skleroseforschung, Münster	astrid.arning@lifa-muenster.de
Arnoldi	Ernst		CLC bio	alykkebak@clcbio.com
Bader	Michael	Prof. Dr.	Max-Delbrück-Center, Berlin	mbader@mdc-berlin.de
Balduin	Melanie	Dr.	chemagen	melanie.balduin@perkinelmer.com
Balschun	Tobias	Dr	Institute for Clinical Molecular Biology, Kiel	t.balschun@ikmb.uni-kiel.de
Bamme	Theresa	Dr.	Hamilton Robotics GmbH	tbamme@hamiltonrobotics.com
Barann	Matthias		IKMB, Kiel	m.barann@ikmb.uni-kiel.de
Barbus	Sebastian	Dr.	German Cancer Research Center (DKFZ), Heidelberg	s.barbus@dkfz.de
Barenboim	Maxim	Ph.D.	Max Planck Institute of Immunobiology, Freiburg	barenboim@immunbio.mpg.de
Bartholémy	Daniel		Sequenom GmbH	vteichmann@sequenom.com
Barysenka	Andrei		Leibniz-Institut für Arterio-skleroseforschung, Münster	andrei.barysenka@lifa-muenster.de
Basmanav	Fitnat Buket	MSc	University of Bonn, Institut of Human Genetics	basmanav@uni-bonn.de
Bauerfeind	Anja	Dr.	MDC-Berlin	a.bauerfeind@mdc-berlin.de
Baurecht	Hansjörg		University of Schleswig-Holstein, Campus Kiel	hbaurecht@dermatology.uni-kiel.de
Beck	Anne	Dr.	Charité - Universitätsmedizin Berlin	anne.beck@charite.de
Becker	Albert	Prof. Dr.	Universität Bonn	albert_becker@uni-bonn.de
Becker	Lore		Helmholtz Zentrum München	lore.becker@helmholtz-muenchen.de
Beckers	Johannes	Priv.-Doz. Dr.	Helmholtz Zentrum München GmbH	beckers@helmholtz-muenchen.de

Surname	First name	Title	Institution	Email
Bentmann	Anke	Dr.	NGFN Management Office	a.bentmann@dkfz.de
Berger	Ina		Uniklinik Ulm	ina.berger@uniklinik-ulm.de
Bergmann	Silke		Helmholtz-Centre for Infections Research, Braunschweig	Silke.Bergmann@helmholtz-hzi.de
Bettecken	Thomas	Dr	Max Planck Institute of Psychiatry, München	bettecken@mpipsykl.mpg.de
Betz	Regina	Prof.	Institute of Human Genetics, Bonn	regina.betz@uni-bonn.de
Bock	Christoph	Dr	Broad Institute, Cambridge, USA	cbock@mpi-inf.mpg.de
Boehm	Markus		Illumina	mboehm@illumina.com
Boelter	Jürgen		Roche Diagnostics Deutschland GmbH	juergen.boelter@roche.com
Boeltz	Harry		Fluidigm B.V.	harry.boeltz@fluidigm.com
Boerno	Stefan		Max-Planck-Institute for Molecular Genetics, Berlin	boerno@molgen.mpg.de
Bolze	Florian		TU München	bolze@wzw.tum.de
Boomgaarden	Inka	Dr	UKSH, Kiel	inka.boomgaarden@uksh.de
Bork	Peer	Prof Dr	European Molecular Biology Laboratory, Heidelberg	peer.bork@embl-heidelberg.de
Bornheim	Roland	Dr.	PT-DLR, Bonn	roland.bornheim@dlr.de
Brettschneider	Falko		Charité, Berlin	falko.brettschneider@charite.de
Breuer	René		ZI Mannheim	rene.breuer@zi-mannheim.de
Bröcker	Felix		Max Planck Institute for Molecular Genetics, Berlin	felixbroecker@gmx.net
Brors	Benedikt	Dr	DKFZ, Heidelberg	b.brors@dkfz.de
Brosius	Jürgen	Prof. Dr.	University of Muenster	brosius@uni-muenster.de
Bruck	Heike	PD Dr.	University Hospital Essen	heike.bruck@uni-due.de
Büchel	Finja		University of Tuebingen	finja.buechel@uni-tuebingen.de
Buchholz	Malte	Dr.	Universität Marburg	malte.buchholz@staff.uni-marburg.de
Cadenas	Cristina	Dr	Leibniz Institut für Arbeitsforschung, Dortmund	cadenas@ifado.de
Carlsson	Thomas	Dr	Goethe University Frankfurt	Carlsson@em.uni-frankfurt.de
Charlet	Katrin		Charité Universitätsmedizin Berlin	katrin.charlet@charite.de
Chavez	Lukas		Max-Planck-Institut für Molekulare Genetik, Berlin	chavez@molgen.mpg.de
Chumduri	Cindrilla	Dr.	Max Plank Institute for Infection Biology, Berlin	chumduri@mpiib-berlin.mpg.de
Clauß	Sebastian	Dr. med.	Klinikum Großhadern, München	sebastian.clauss@med.uni-muenchen.de
Conrad	Ulrike	Dipl. Biol.	German Cancer Research Center - DKFZ, Heidelberg	u.conrad@dkfz.de
Dabrowski	Piotr Wojtek		Robert Koch-Institut, Berlin	dabrowskiw@rki.de
Daser	Angelika	Dr.	Fertility Center Wiesbaden	daser@mrc-lmb.cam.ac.uk
Daskalaki	Andriani	Dr.	Max Planck Institute for Molecular Genetics, Berlin	daskalak@molgen.mpg.de
de Visser	Karin	Dr	The Netherlands Cancer Institute, Amsterdam, NL	k.d.visser@nki.nl
Degenhardt	Franziska		Inst of Human Genetics, Bonn	franziska.degenhardt@uni-bonn.de
Deussing	Jan	Dr	Max Planck Institute of Psychiatry, München	deussing@mpipsykl.mpg.de

Surname	First name	Title	Institution	Email
Diepenbroek	Meike		Institute of Human Genetics, Tübingen	meike.diepenbroek@gmx.net
Dittmer	Alexandra	Dr.	LMU, München	dittmer@lmb.uni-muenchen.de
Dölken	Lars	Dr	Addenbrooke´s Hospital, Cambridge, UK	doelken@lmb.uni-muenchen.de
Dörge	Petra	Dr	University Medical Centre Schleswig-Holstein, Campus Kiel	p.breithaupt@pediatrics.uni-kiel.de
Dosoki	Heba	phd student	Ludwig Boltzmann Institute for Cell Biology, Münster	hebasalah40@gmail.com
Dreher	Felix		MPI for Molecular Genetics, Berlin	dreher@molgen.mpg.de
Drewes	Thomas	Dr.	University Hospital Heidelberg	thomas.drewes@med.uni-heidelberg.de
Eckhard	Jamina		Charité Campus Buch	eckhard@mdc-berlin.de
Eden	Matthias	MD	Iniversity Hospital Schleswig Holstein, Kiel	matthias.eden@uk-sh.de
Eigenbrod	Ole		Max-Planck-Institute for Molecular Genetics, Berlin	eigenbro@molgen.mpg.de
Ellinghaus	Eva		Christian-Albrechts-University Kiel	e.ellinghaus@ikmb.uni-kiel.de
ElSharawy	Abdou	Dr.	Institute of Clinical Molecular Biology (ICMB), Kiel	a.sharawy@mucosa.de
Endres	Kristina	Dr.	University Medical Centre, Mainz	endres_k@psychiatrie.klinik.uni-mainz.de
Erdmann	Jeanette	Univ.-Prof.	Universität zu Lübeck	j.erdmann@cardiogenics.eu
Erdogan	Fikret	Dr.	ATLAS Biolabs GmbH	erdogan@atlas-biolabs.com
Erhard	Florian		LMU München	Florian.Erhard@bio.ifi.lmu.de
Erk	Susanne	Dr.	Charité Universitätsmedizin Berlin, Campus Mitte	susanne.erk@charite.de
Ernst	Florian		Universität Greifswald	ernst@uni-greifswald.de
Esparza Gordillo	Jorge	Dr	Charité University Medicine, Berlin	jesparza@mdc-berlin.de
Esser	Daniela		Christian-Albrechts-Universität, Kiel	d.esser@ikmb.uni-kiel.de
Eufinger	Jan	Dr.	DKFZ, Heidelberg	j.eufinger@dkfz.de
Farrall	Alexandra	Dr	Max Planck Institute for Molecular Genetics, Berlin	farrall@molgen.mpg.de
Ferlinz	Astrid	Dr.	Life Technologies	Astrid.Ferlinz@lifetech.com
Fischer	Annegret	Dr.	Christian-Albrechs Universität, Kiel	a.fischer@ikmb.uni-kiel.de
Fischer	Axel		Max-Planck-Institute for Molecular Genetics, Berlin	afischer@molgen.mpg.de
Fischer	Matthias	PD Dr.	University of Cologne	matthias.fischer@uk-koeln.de
Fisher	Eva	Dr	Robert Koch-Institut, Berlin	fishere@rki.de
Forster	Michael		Christian-Albrechts-University Kiel	m.forster@ikmb.uni-kiel.de
Frank	Josef		CIMH, Mannheim	jfrank@zi-mannheim.de
Franke	Andre	Prof. Dr.	Christian-Albrechts-University Kiel	admin2@ikmb.uni-kiel.de
Frommolt	Peter	Dr	Universität zu Köln	peter.frommolt@uni-koeln.de

Surname	First name	Title	Institution	Email
Fuchs	Helmut	Dr.	Helmholtz Zentrum München	hfuchs@helmholtz-muenchen.de
Fuhrmann	Jens	Dr.	metanomics GmbH	jens.fuhrmann@metanomics.de
Funk	Edgar	Dr.	Complete Genomics Inc.	efunk@completegenomics.com
Garratt	Alistair	Dr.	Max-Delbrueck-Center for Molecular Medicine, Berlin	agarratt@mdc-berlin.de
Garrett	Lillian	Dr	Helmholtz Zentrum München	lillian.garrett@helmholtz-muenchen.de
Gieger	Christian	Dr	Helmholtz Zentrum München	christian.gieger@helmholtz-muenchen.de
Gispert	Suzana		Goethe University, Frankfurt am Main	gispert-sanchez@em.uni-frankfurt.de
Gloeckner	Christian Johannes	Dr.	Helmholtz-Zentrum München	j.gloeckner@helmholtz-muenchen.de
Glowinski	Frithjof		MPI for Infection Biology, Berlin	glowinski@mpiib-berlin.mpg.de
Gohlke	Henning	Dr.	Sequenom GmbH	hgohlke@sequenom.com
Gonzalez	Erik		Max Planck Institute for Infection Biology, Berlin	gonzalez@mpiib-berlin.mpg.de
Goraga	Zemelak	Dr.	Humboldt Universität zu Berlin	zemelaks@yahoo.com
Grabowski	Katja		Charité, Berlin	katja.grabowski@charite.de
Graf	Elisabeth		Helmholtz Zentrum München	Elisabeth.Graf@helmholtz-muenchen.de
Gress	Thomas	Prof. Dr.	University of Marburg	gress@med.uni-marburg.de
Grimm	Christina	Dr.	Max Planck Institute for Molecular Genetics, Berlin	grimm@molgen.mpg.de
Grimminger	Tanja		University of Bonn	tgrimminger@googlemail.com
Groop	Leif	Prof	Lund University, Malmö, Sweden	Leif.Groop@med.lu.se
Grün	Joachim R.	Dr.	Deutsches Rheumaforschungszentrum (DRFZ), Berlin	Gruen@DRFZ.de
Grünewald	Anne	PhD	University of Lübeck	anne.gruenewald@neuro.uni-luebeck.de
Guan	Kaomei	PD Dr.	Georg-August-University of Göttingen	kguan@med.uni-goettingen.de
Gundel	Silke	Dr.	PT-DLR, Bonn	silke.gundel@dlr.de
Gut	Ivo	Dr.	Centro Nacional de Análisis Genómico (CNAG), Barcelona	igut@pcb.ub.cat; kslopez@pcb.ub.cat
Haas	Jürgen	Prof.	LMU München, Max-von-Pettenkofer Institut	haas@lmb.uni-muenchen.de
Haas	Stefan	Dr	Max Planck Institute for Molecular Genetics, Berlin	haas@molgen.mpg.de
Hache	Hendrik	Dr	MPI for Molecular Genetics, Berlin	hache@molgen.mpg.de
Haenisch	Britta	Dr	University of Bonn	haenisch@uni-bonn.de
Hagn	Michael	Dr	Helmholtz Zentrum München	michael.hagn@helmholtz-muenchen.de
Hahn	Meinhard	Dr.	LKA Niedersachsen	meinhard.hahn@polizei.niedersachsen.de
Hallung	Nicole		MPI-MG, Berlin	hallung@molgen.mpg.de

Surname	First name	Title	Institution	Email
Hans	Wolfgang	Dr	Helmholtz Zentrum München	wolfgang.hans@helmholtz-muenchen.de
Hansen	Jens	Dr.	Helmholtz Zentrum München	hansen@helmholtz-muenchen.de
Hantschel	Claudia		Humboldt-Universität zu Berlin	claudia.hantschel@agrar.hu-berlin.de
Hardt	Christopher		Max Planck Institute for Molecular Genetics, Berlin	hardt@molgen.mpg.de
Häsler	Robert	PhD	Christian Albrechts University of Kiel	r.haesler@mucosa.de
Haupt	Armin		Max Planck Institute for Molecular Genetics, Berlin	haupt_a@molgen.mpg.de
Hebebrand	Johannes	Prof. Dr.	LVR-Klinikum Essen, University Duibsurg-Essen	johannes.hebebrand@uni-due.de
Hedrich	Ulrike	Dr.	Hertie Institute, University of Tuebingen	ulrike.hedrich@uni-tuebingen.de
Heim	Katharina		Helmholtz Zentrum München	katharina.heim@helmholtz-muenchen.de
Heinig	Matthias		Max-Planck-Institute for Molecular Genetics, Berlin	heinig@molgen.mpg.de
Hennings	Johannes	Dr.	Max Planck Institute of Psychiatry, München	hennings@mpipsykl.mpg.de
Herms	Stefan		Life&Brain	sherms@lifeandbrain.com
Herrmann	Bernhard G.	Prof. Dr.	Max Planck Institute for Molecular Genetics, Berlin	herrmann@molgen.mpg.de
Herwig	Ralf	Dr	Max Planck Institute for Molecular Genetics, Berlin	herwig@molgen.mpg.de
Heubner	Dagmar	Dr.	LGC Genomics	dagmar.heubner@lgcgenomics.com
Hoehe	Margret	Dr.	Max Planck Institute for Molecular Genetics, Berlin	hoehe@molgen.mpg.de
Hoffmann	Per	Dr. rer. nat.	University of Bonn	p.hoffmann@uni-bonn.de
Hoffmann	Kathrin		Caliper Life Sciences GmbH	kathrin.hoffmann@caliperls.com
Höglinger	Günter	Prof.	Philipps University, Marburg	hoegling@med.uni-marburg.de
Hoheisel	Jörg	Dr.	DKFZ, Heidelberg	j.hoheisel@dkfz.de
Höllerhage	Matthias	Dr.	Philipps-University Marburg	m.hoellerhage@exp-neuro.de
Hölter-Koch	Sabine	Dr.	Helmholtz Zentrum München	hoelter@helmholtz-muenchen.de
Homuth	Georg	Dr	University Medicine Greifswald	georg.homuth@uni-greifswald.de
Honstein	Tatjana		University of Marburg	honstein@staff.uni-marburg.de
Horn	Patrick	Dr.	Heidelberg University	patrick.horn@med.uni-heidelberg.de
Horpaopan	Sukanya		Institute of Human Genetics, Bonn	s6suhorp@uni-bonn.de
Horsch	Marion	Dr	Helmholtz Zentrum München	horsch@helmholtz-muenchen.de
Hrabě de Angelis	Martin	Prof. Dr.	Helmholtz Zentrum München	hrabe@helmholtz-muenchen.de
Hübner	Norbert		MDC, Berlin	nhuebner@mdc-berlin.de
Huebsch	Thomas	Dr.	Max Planck Institute for Molecular Genetics, Berlin	huebsch@molgen.mpg.de
Huhn	Gabriele	Dpl.-Kffr.	University of Luebeck	g.huhn@cardiogenics.eu

Surname	First name	Title	Institution	Email
Huse	Klaus		Leibniz Institute for Age Research, Jena	khuse@fli-leibniz.de
Hussong	Michelle		Max Planck Institut für molekulare Genetik, Berlin	hussong@molgen.mpg.de
Illig	Thomas	Prof. Dr.	Helmholtz Zentrum München	illig@helmholtz-muenchen.de
Isau	Melanie		Max Planck Institute for moleculare genetics, Berlin	isau@molgen.mpg.de
Isbrandt	Dirk	Prof. Dr.	UMC Hamburg-Eppendorf	isbrandt@uke.de
Janas	Eva	Dr	Helmholtz Center Munich	eva.janas@helmholtz-muenchen.de
Jang	Seon-Hi Julia		Max Planck Institute for Molecular Genetics, Berlin	jang@molgen.mpg.de
Jankowski	Joachim	Univ.-Prof. Dr.	Charité, Berlin	Joachim.Jankowski@charite.de
Jankowski	Vera	Dr.	Charité, Berlin	Vera.Jankowski@charite.de
Jansen	Katja	Dr.	Illumina Ltd	kjansen@illumina.com
Johnson	Lindsey		Charité Universitätsmedizin Berlin	lindsey.erman@charite.de
Joo	Sang	MD	Houston, USA	joosangbai@gmail.com
Joo	Jinsoo		BNIT, San Francisco, USA	JCubed123@yahoo.com
Jozefczuk	Justyna	Dr	Max-Planck Institute for Molecular Genetics, Berlin	jagodzin@molgen.mpg.de
Junker	Barbara	PD Dr.	PT-DLR, Bonn	barbara.junker@dlr.de
Just	Steffen	Dr.	University of Ulm	steffen.just@uniklinik-ulm.de
Jutzi	Tanja	Dr.	NGFN Management Office	t.jutzi@dkfz.de
Kääb	Stefan	Prof. Dr.	Ludwig-Maximilians University, Munich	skaab@med.lmu.de
Kähler	Christian		MPI Molecular Genetics, Berlin	kaehler@molgen.mpg.de
Kalscheuer	Vera	Dr.	Max Planck Institute for Molecular Genetics, Berlin	kalscheu@molgen.mpg.de
Kamburov	Atanas		Max Planck Institute for Molecular Genetics, Berlin	kamburov@molgen.mpg.de
Karas	Holger		CLC bio	hkaras@clcbio.com
Karbalai	Nazanin		MPI of Psychiatry, München	nazanin@mpipsykl.mpg.de
Katus	Hugo	Prof	Universitätsklinikum Heidelberg	hugo.katus@med.uni-heidelberg.de
Keck	Andreas	Dr.	Illumina	akeck@illumina.com
Kelkenberg-Schade	Sabine		DKFZ, Heidelberg	s.kelkenberg@dkfz.de
Kempf	Tore	Dr.	DKFZ, Heidelberg	t.kempf@dkfz.de
Kerick	Martin	Dr	MPI for molekulare Genetik, Berlin	mkerick@molgen.mpg.de
Kerscher	Tamara		Charité Campus Buch	t.kerscher@mdc-berlin.de
Kessler	Thorsten	Dr. med.	Universitaet zu Luebeck	thorsten.kessler@uk-sh.de
Kessler	Thomas		MPIMG, Berlin	kessler@molgen.mpg.de
Kieckbusch	Kristina		Universitätsklinikum Essen	kristina.kieckbusch@rub.de
Kisser	Agnes	Dr	Max Planck Institute for Molecular Genetics, Berlin	kisser@molgen.mpg.de
Kistler	Martin		Helmholtzzentrum München	martin.kistler@helmholtz-muenchen.de
Klein-Rodewald	Tanja	Dr	Helmholtz Center Munich	tanja.klein@helmholtz-muenchen.de

Surname	First name	Title	Institution	Email
Klingenspor	Martin	Prof.	Technische Universität München	mk@tum.de
Kloiber	Stefan	Dr	Max-Planck-Institut für Psychiatry, München	stkloiber@mpipsykl.mpg.de
Klopp	Norman	Dr.	Helmholtz Zentrum München	klopp@helmholtz-muenchen.de
Knoll	Nadja		University Duisburg-Essen	Nadja.knoll@uni-due.de
Koeppel	Max		MPI for Infection Biology, Berlin	m_koeppel@web.de
Konczwald	Antonia		chemagen	antonia.konczwald@perkinelmer.com
Kong	Bo	Dr.	Klinikum rechts der Isar, Technical University Munich	kongbo81@hotmail.com
Kosiura	Anna		Max-Planck-Institute for Molecular Genetics, Berlin	kosiura@molgen.mpg.de
Kovacsovics	Alexander		Max-Planck-Institute for Molecular Genetics, Berlin	kovacsov@molgen.mpg.de
Kramer	Marcel	Dr.	Universitätsklinikum Jena	Marcel.Kramer@med.uni-jena.de
Krastev	Dragomir	Dr.	MPI-CBG, Dresden	krastev@mpi-cbg.de
Krebiehl	Guido	Dr.	Labor für Funktionelle Neurogenomik, Tübingen	guido.krebiehl@uni-tuebingen.de
Kretschmer	Axel	Dr.	Bayer Pharma AG	axel.kretschmer@bayer.com
Kreutz	Reinhold	Prof.Dr.	Charite - Universtätsmedizin Berlin	reinhold.kreutz@charite.de
Kriegel	Ann-Kathrin		University of Cologne	a.kriegel@uni-koeln.de
Kröger	Stefan		Humboldt-Universität zu Berlin	kroeger@informatik.hu-berlin.de
Kuch	Christine	Dr.	Roche Diagnostics Deutschland GmbH	christine.kuch@roche.com
Kühn	Alexander	Dr.	Max-Planck-Institute for Molecular Genetics, Berlin	kuehn_a@molgen.mpg.de
Kumar	Kishore	Dr	Lübeck University	kkum4618@uni.sydney.edu.au
Kumer	Nada		Max Planck Institute for Molecular Genetics, Berlin	kumer@molgen.mpg.de
Kuner	Ruprecht	Dr.	DKFZ / NCT, Heidelberg	r.kuner@dkfz.de
Kurek	Roman	Dr.	Exiqon A/S	rok@exiqon.com
Kurtz	Tanja		Max Planck Institute for Molecular Genetics, Berlin	kurtz@molgen.mpg.de
Kurz	Thorsten	Dr.	GATC Biotech AG	t.kurz@gatc-biotech.com
Lal	Dennis	MSc	University of Cologne	lald@uni-koeln.de
Lampert	Johanna	Dr.	NGFN Management Office	j.lampert@dkfz.de
Lange	Bodo	PD Dr	Max Planck Institute for Molecular Genetics, Berlin	lange_b@molgen.mpg.de
Lawerenz	Chris		DKFZ, Heidelberg	c.lawerenz@dkfz.de
Lee	Jennifer	Dr.	Life & Brain Center, Bonn	jlee@uni-bonn.de
Lee	Young-Ae		MDC, Berlin	yolee@mdc-berlin.de
Lehrach	Hans	Prof. Dr.	Max Planck Institute for Molecular Genetics, Berlin	lehrach@molgen.mpg.de
Lengeling	Andreas	Dr	University of Edinburgh, UK	Andreas.Lengeling@ed.ac.uk
Leser	Ulf	Prof. Dr.	Humboldt-Universität zu Berlin	leser@informatik.hu-berlin.de
Li	Jian		Max-Planck-Institute for Molecular Genetics, Berlin	jianli@molgen.mpg.de
Lichtenberg	Hella	Dr.	BMBF, Berlin	hella.lichtenberg@bmbf.bund.de

Surname	First name	Title	Institution	Email
Lincoln	Steve	Dr.	Complete Genomics Inc.	slincoln@completegenomics.com
Lindner	Martin S.		Robert Koch-Institut, Berlin	lindnerm@rki.de
Lindpaintner	Klaus	Prof	Vice President Research & Development, SDIX, USA	klindpaintner@sdix.com
Linser	Matthias	B.Sc.	Max-Planck-Institute for Molecular Genetics, Berlin	linser@molgen.mpg.de
Liu	Sha	M.Sc.	Charité Universitätsmedizin Berlin, Institute of Pathology	sha.liu@charite.de
Lohmann	Katja	Dr.	University of Luebeck	katja.lohmann@neuro.uni-luebeck.de
Löwer	Martin	Dr	TRON	martin.loewer@tron-mainz.de
Lucae	Susanne		Max Planck Institute of Psychiatry, München	lucae@mpipsykl.mpg.de
Madsen	Kim		CLC bio A/S	kmadsen@clcbio.com
Malik	Arif	Dr.	MicroDiscovery GmbH	arif.malik@microdiscovery.de
Maljevic	Snezana	Dr	Hertie Institute for Clinical Brain Research, Tübingen	snezana.maljevic@uni-tuebingen.de
Marquis	Eve	Dr	Fluidigm Europe	eve.marquis@fluidigm.com
Maschke-Dutz	Elisabeth		Max-Planck-Institute for Molecular Genetics, Berlin	maschke@molgen.mpg.de
Matanovic	Anja		Charité Campus Buch	anja.matanovic@mdc-berlin.de
Mattheisen	Manuel	MD	University of Bonn	mmattheisen@uni-bonn.de
McEwen	Gayle	Dr	Max Planck Insititute for Molecular Genetics, Berlin	mcewen@molgen.mpg.de
Medack	Anja		Universität zu Lübeck	anja.medack@uk-sh.de
Meder	Benjamin	Dr	University Heidelberg	benjamin.meder@med.uni-heidelberg.de
Megges	Matthias		Max Planck Institute for Molecular Genetics, Berlin	megges@molgen.mpg.de
Meier	Sandra	MSc	Central Institute of Mental Health, Mannheim	sandra.meier@zi-mannheim.de
Meitinger	Thomas	Prof. Dr.	Helmholtz Zentrum München	meitinger@helmholtz-muenchen.de
Meixner	Andrea		University of Tuebingen	andrea.meixner@uni-tuebingen.de
Melchisedech	Sandra		University of Marburg	melchise@staff.uni-marburg.de
Menssing	Ole		Illumina GmbH	omenssing@illumina.com
Merlo	Kevin	Phd Student	Robert Koch-Institut, Berlin	MerloK@rki.de
Mers	Wolfgang		Illumina GmbH	wmers@illumina.com
Merseburg	Andrea	M.Sc.	Zentrum für Molekulare Neurobiologie Hamburg	andrea.merseburg@enp.org
Michel	Dian	Dr.	Freie Universität Berlin	dian.michel@fu-berlin.de
Michel	Geert	Dr	Charité, Berlin	geert.michel@charite.de
Micklich	Kateryna		Helmholtz Zentrum München	kateryna.micklich@helmholtz-muenchen.de
Miehle	Anita		NGFN Management Office	a.miehle@dkfz.de
Miró	Xavier	Dr	Universitätsklinikum Bonn	xmiro@uni-bonn.de
Mittag	Florian		University of Tuebingen	florian.mittag@uni-tuebingen.de
Mlody	Barbara		Max Planck Institute for Molecular Genetics, Berlin	mlody@molgen.mpg.de
Moehrle	Axel	Dr	4titude Ltd.	axelm@4ti.co.uk
Morelli	Giovanna	Dr.	Max-Planck-Institut für molekulare Genetik, Berlin	Morelli@molgen.mpg.de
Moritz	Philipp		University of Luebeck	philipp.rumpf@uksh.de

Surname	First name	Title	Institution	Email
Mössner	Rainald	PD Dr.	University of Bonn	rainald.moessner@ukb.uni-bonn.de
Mueller	Christian		UKE - Hamburg	christian_m@gmx.net
Mühleisen	Thomas	Dr.	Institute of Human Genetics, University of Bonn	thomas.muehleisen@uni-bonn.de
Müller	Fabian		Max Planck Institute for Informatics, Saarbrücken	fmueller@mpi-inf.mpg.de
Müller	Julia	Dr.	Deutsches Krebsforschungs-zentrum, Heidelberg	julia.mueller@dkfz-heidelberg.de
Müller	Hubert	Dr.	Ascenion GmbH	mueller@ascenion.de
Muradyan	Artur	Dr.	Max Planck Institute for Molecular Genetics, Berlin	muradyan@molgen.mpg.de
Nassar	Mostafa		Humboldt Universitat zu Berlin	mostnassar@yahoo.com
Naton	Beatrix	Dr.	Helmholtz Zentrum München	beatrix.naton@helmholtz-muenchen.de
Nieratschker	Vanessa	Dr. rer. nat.	CIMH, Mannheim	vanessa.nieratschker@zi-mannheim.de
Niesler	Beate	PD Dr. rer. nat.	University of Heidelberg	beate.niesler@med.uni-heidelberg.de
Nietfeld	Wilfried	Dr	Max-Planck-Institute for Molecular Genetics, Berlin	Nietfeld@molgen.mpg.de
Nitzsche	Anja		MPI-CBG, Dresden	anitzsch@mpi-cbg.de
Nöthen	Markus	Prof. Dr.	University of Bonn	markus.noethen@uni-bonn.de
Nothnagel	Michael	Dr.	Christian-Albrechts University, Kiel	nothnagel@medinfo.uni-kiel.de
Nürnberg	Peter	Prof. Dr.	University of Cologne	nuernberg@uni-koeln.de
Nürnberger	Asja		Max-Planck-Institute for Molecular Genetics, Berlin	nuernber@molgen.mpg.de
Ojeda Echevarria	Francisco		University Medical Center Hamburg-Eppendorf	f.ojeda-echevarria@uke.de
Okonechnikov	Konstantin		Max Planck Institute For Infection Biology, Berlin	k.okonechnikov@gmail.com
Otte	David-Marian	Dr.	University of Bonn, Molecular Psychiatry	d.otte@uni-bonn.de
Pandey	Vikash		Max Planck Institute of Molecular Genetics, Berlin	vpandey@molgen.mpg.de
Patzel	Eva		Universitätsklinikum Ulm	eva.patzel@uniklinik-ulm.de
Paulsen	Maren	Dr.	Christian-Albrechts-University Kiel, UK-SH Campus Kiel	m.paulsen@ikmb.uni-kiel.de
Pernhorst	Katharina		Universität Bonn	kpernhor@uni-bonn.de
Perrot	Andreas	Dipl.-Ing.	Charité-Universitätsmedizin Berlin	andreas.perrot@charite.de
Petersen	Britt-Sabina		Christian-Albrechts-University, Kiel	b.petersen@ikmb.uni-kiel.de
Pfenninger	Cosima	Dr.	PT-DLR, Bonn	cosima.pfenninger@dlr.de
Platzer	Matthias	PD Dr.	FLI Jena	mplatzer@fli-leibniz.de
Poshcmann	Gereon	Dr.	Ruhr-Universität Bochum	gereon.poschmann@rub.de
Potter	Derek		NanoString Technologies	dpotter@nanostring.com
Preuss	Christoph		LIFA Muenster	christoph.preuss@lifa-muenster.de
Priebe	Lutz		Institute of Human Genetics, University of Bonn	lpriebe@uni-bonn.de

Surname	First name	Title	Institution	Email
Prigione	Alessandro	Dr	Max-Planck Institute for Molecular Genetics, Berlin	prigione@molgen.mpg.de
Pruess	Maik		Affymetrix	maik_pruess@affymetrix.com
Puk	Oliver		Helmholtzzentrum München	oliver.puk@helmholtz-muenchen.de
Pütter	Carolin		Universität Duisburg-Essen	carolin.puetter@uk-essen.de
Quedenau	Claudia		MPI f. Molekulare Genetik, Berlin	queden_c@molgen.mpg.de
Raabe	Carsten		Universtaet Muenster	raabec@uni-muenster.de
Rácz	Ildikó	PD PhD	University of Bonn	iracz@uni-bonn.de
Radlwimmer	Bernhard	Dr	German Cancer Research Center, Heidelberg	b.radlwimmer@dkfz.de
Raskó	Tamás	Dr	MDC-Berlin	tamas.rasko@mdc-berlin.de
Ratholb	Brigit	Dr.	Ludwig-Maximilians-Universität München	birgit.rathkolb@helmholtz-muenchen.de
Raue	Stefan		University of Tübingen	studium@sraue.de
Rawal	Rajesh	Dr.	Helmholtz Zentrum München	rajesh.rawal@helmholtz-muenchen.de
Rehbein	Grit	Dr.	Medizinische Fakultät, MLU, Halle	grit.rehbein@medizin.uni-halle.de
Reinhardt	Sven		University Medical Centre Mainz	reinhardt_s@psychiatrie.klinik.uni-mainz.de
Reinhardt	Richard		MPI for Plant Breeding Research, Köln	rr@mpipz.mpg.de
Reinke	Peter			
Renard	Bernhard	Dr.	Robert Koch-Institut, Berlin	RenardB@rki.de
Rhein	Peter	Dr.	Charité, Berlin	peter.rhein@charite.de
Riechers	Sean-Patrick		MDC, Berlin	patrick.riechers@mdc-berlin.de
Riemenschneider	Mona		Leibniz-Institut für Arterioskleroseforschung, Münster	mona.riemenschneider@lifa-muenster.de
Riemenschneider	Matthias	Prof. Dr.	Universität des Saarlandes	matthias.riemenschneider@uks.eu
Rink	Nadine		TU München	nadine.rink@mytum.de
Röhr	Christina		Max Planck Institute for Molecular Genetics, Berlin	roehr@molgen.mpg.de
Ropers	Hans-Hilger	Prof	Max Planck Institute for Molecular Genetics, Berlin	ropers@molgen.mpg.de
Röpke	Albrecht	Dr.	Institut für Humangenetik, Universität Münster	aroepke@uni-muenster.de
Rosenstiel	Philip	Prof. Dr.	Institute of Clinical Molecular Biology, CAU, Kiel	p.rosenstiel@mucosa.de
Rottbauer	Wolfgang	Prof. Dr. med.	Universitätsklinikum Ulm	sekretariat.rottbauer@uniklinik-ulm.de
Rozhdestvensky	Timofey	Dr	Institute of Experimental Pathology, University of Muenster	rozhdest@uni-muenster.de
Rozman	Jan	Dr.	Helmholtz Centre Munich	jan.rozman@helmholtz-muenchen.de
Rueth	Marieke	Dipl.Ing.	EXcorLab GmbH	marieke.rueth@excorlab.de
Rühle	Frank	Dr.	Leibniz-Institut für Arterioskleroseforschung (LIF), München	frank.ruehle@lifa-muenster.de
Rujescu	Dan	Prof.	University of Munich	Dan.Rujescu@med.uni-muenchen.de
Russ	Jenny		Max Delbrück Center, Berlin	jenny.russ@mdc-berlin.de

Surname	First name	Title	Institution	Email
Rüther	Andreas	Dr.	Christian-Albrechts-Universität zu Kiel	a.ruether@mucosa.de
Saar	Kathrin		MDC, Berlin	ksaar@mdc-berlin.de
Sander	Thomas	Dr.	University of Cologne	sandert@uni-koeln.de
Sauer	Sascha	Dr.	Max-Planck-Institute for Molecular Genetics, Berlin	sauer@molgen.mpg.de
Schäfer	Arne	Dr. rer. nat.	Christian-Albrechts-University Kiel	a.schaefer@ikmb.uni-kiel.de
Schäfer	Reinhold	Prof.	Charité, Berlin	reinhold.schaefer@charite.de
Schauder	Frank	Dr. med.	BNI Hamburg	Tropenbuch@web.de
Schechinger	Barbara	Dr.	Illumina GmbH	bschechinger@illumina.com
Schilhabel	M		CAU, Kiel	m.schilhabel@ikmb.uni-kiel.de
Schlaermann	Philipp		Max Planck Institute for Infection Biology, Berlin	Philipp.Schlaermann@mpiib-berlin.mpg.de
Schlueter	Carsten	Dr.	Roche Diagnostics Deutschland GmbH	carsten.schlueter@roche.com
Schmitz	Goesta		Affymetrix	goesta_schmitz@affymetrix.com
Schnieders	Birgit	Dr.	Federal Ministry of Health	Birgit.Schnieders@bmg.bund.de
Schnölzer	Martina		DKFZ, Heidelberg	m.schnoelzer@dkfz.de
Schoch-McGovern	Susanne	Prof. Dr.	Universität Bonn	susanne.schoch@uni-bonn.de
Schollmeyer	Martin	Dr.	Sigma Aldrich	Martin.Schollmeyer@sial.com
Schramm	Alexander	PD Dr.	University Hospital Essen	alexander.schramm@uni-due.de
Schreiber	Stefan	Prof.	Christian-Albrechts-University Kiel	s.schreiber@mucosa.de
Schubert	Julian		Hertie Instiute for Clinical Brain Research, Tübingen	julian.schubert@uni-tuebingen.de
Schuchhardt	Johannes	Dr.	MicroDiscovery GmbH	johannes.schuchhardt@microdiscovery.de
Schuermann	Annette	Prof. Dr.	German Institute of Human Nutrition, Potsdam-Rehbrücke	schuermann@dife.de
Schulte	Claudia		Hertie Institute, Tübingen	claudia.schulte@uni-tuebingen.de
Schulte	Leonard		Charité, Berlin	leonard.schulte@charite.de
Schulz	Nadja		German Institute for Human Nutrition, Nuthetal	nadja.schulz@dife.de
Schulz	Angela	Dr.	Charité - Universitätsmedizin Berlin	angela-martina.schulz@charite.de
Schulz	Anna		Charité, Berlin	anna.schulz@charite.de
Schunkert	Heribert	Prof. Dr.	UKSH, Campus Lübeck	Heribert.Schunkert@uksh.de
Schurmann	Claudia	Dipl.-Biomath.	University Medicine Greifswald	claudia.schurmann@uni-greifswald.de
Schütt	Antje		TMF e.V.	antje.schuett@tmf-ev.de
Schwarz	Jana Marie		Charité Berlin	jana-marie.schwarz@charite.de
Schweiger	Michal Ruth	Dr.Dr.	Max Planck Institute for Molecular Genetics, Berlin	mschweig@molgen.mpg.de
Seelow	Dominik		Charité, Berlin	dominik.seelow@charite.de
Serpi	Raisa	Dr	Helmholtz Center Munich	calzada@helmholtz-muenchen.de
Seufferlein	Thomas	Prof. Dr.	Universitätsklinikum Halle	thomas.seufferlein@uk-halle.de
Sharif	Nawid		Charité, Berlin	ahmad-nawid.sharif@charite.de
Siddiqui	Roman	Dr.	TMF	roman.siddiqui@tmf-ev.de

Surname	First name	Title	Institution	Email
Siedek	Florian		University of Bonn	siedek@uni-bonn.de
Simon	Josef		Universitätsklinikum Regensburg	josef.simon@klinik.uni-regensburg.de
Sommer	Wolfgang	Dr.	Central Institute of Mental Health, Mannheim	wolfgang.sommer@zi-mannheim.de
Spanagel	Rainer	Prof. Dr.	Central Institute of Mental Health, Mannheim	rainer.spanagel@zi-mannheim.de
Spilker	Dominik	Dr.	Beckman Coulter Genomics	dspilker@beckman.com
Stadler	Margit	Dr.	Fluidigm Europe BV	margit.stadler@fluidigm.com
Stangel	Daniela		Klinikum rechts der Isar, TU München	daniela.stangel@gmx.de
Stelzl	Ulrich		Max Planck Institute for Molecular Genetics, Berlin	stelzl@molgen.mpg.de
Stephan	Harald	Dr	University Children´s Hospital Essen	harald.stephan@uni-due.de
Stermann	Alexander		Universitätsmedizin Greifswald	alexander.stermann@uni-greifswald.de
Stieber	Christiane	Dr.	Institute of Human Genetics, Bonn	cstieber@uni-bonn.de
Stoll	Monika	Prof. Dr.	LIFA Muenster	monika.stoll@lifa-muenster.de
Strehle	Martin		Helmholtz Zentrum München	martin.strehle@helmholtz-muenchen.de
Strohmaier	Jana		Central Institute of Mental Health, Mannheim	jana.strohmaier@zi-mannheim.de
Strom	Tim M	Dr.	Helmholtz Zentrum München	timstrom@helmholtz-muenchen.de
Stühler	Kai	Prof. Dr.	Heinrich-Heine-Universität, Düsseldorf	kai.stuehler@hhu.de
Stunnenberg	Henk	Prof	Nijmegen Centre for Molecular Life Sciences, Nijmegen, NL	H.Stunnenberg@ncmls.ru.nl
Sudbrak	Ralf	Dr.	MPI für Molekulare Genetik, Berlin	sudbrak@molgen.mpg.de
Suk	Eun-Kyung	Dr.	Max Planck Institute for Molecular Genetics, Berlin	suk@molgen.mpg.de
Sültmann	Holger	PD Dr	DKFZ and NCT	h.sueltmann@dkfz.de
Temme	Claudia		Universitätsklinikum Halle	claudia.temme@uk-halle.de
Teske	Anja	Dr	Complete Genomics Inc.	ateske@completegenomics.com
Thomas	Roman	Dr.	Max-Planck Institut f. neurol. Forschung, Köln	nini@nf.mpg.de
Thor	Theresa		University Children`s Hospital	Theresa.Thor@uk-essen.de
Timmermann	Bernd	Dr	Max Planck Institute for molecular Genetics, Berlin	timmerma@molgen.mpg.de
Tönjes	Martje	Dr.	German Cancer Research Center (DKFZ), Heidelberg	m.toenjes@dkfz.de
Treise	Irina		Helmholtz-Zentrum München	irina.treise@helmholtz-muenchen.de
Treutlein	Jens	Dr	CIMH, Mannheim	jens.treutlein@zi-mannheim.de
Truss	Matthias	Dr	Charite, Berlin	matthias.truss@charite.de
Uebachs	Mischa	Dr	University of Bonn	m.uebachs@uni-bonn.de
Ungethüm	Ute	Dr.	Charité, Berlin	ute.ungethuem@charite.de

Surname	First name	Title	Institution	Email
Unland	Johannes		Charité, Berlin	johannes.unland@charite.de
van Duijn	Cornelia M.	Prof	Erasmus Medical Center, Rotterdam, NL	c.vanduijn@erasmusmc.nl
van Loon	Gunhild		Institute of Human Genetics, Bonn	gvanloon@uni-bonn.de
Veltman	Joris	Prof	Radboud University Medical Centre Nijmegen, NL	J.Veltman@antrg.umcn.nl
Vingron	Martin	Prof. Dr.	MPI for Molecular Genetics, Berlin	vinoffic@molgen.mpg.de
Vladimirova	Valentina	PhD	University of Bonn	valentina.vladimirova@ukb.uni-bonn.de
Vogel	Heike		German Institute for Human Nutrition, Nuthetal	heikevogel@dife.de
Vogelsang	Ralph	Dr	Pacific Biosciences	rvogelsang@pacificbiosciences.com
Vogl	Silvia		Charité, Berlin	silvia.vogl@charite.de
Vogt Weisenhorn	Daniela	Dr.	Helmholtz Zentrum München	daniela.vogt@helmholtz-muenchen.de
Voigt	Aaron	Dr.	University Medical Centre, RWTH Aachen	avoigt@ukaachen.de
Volckmar	Anna-Lena		University of Duisburg-Essen	anna-lena.volckmar@uni-due.de
von Melchner	Harald	Prof. Dr.	University of Frankfurt, Medical School	melchner@em.uni-frankfurt.de
von Witsch	Matthias	Dr.	PT-DLR, Bonn	matthias.vonwitsch@dlr.de
Wadzack	Joerg	Dr.	Freie Universität Berlin	joerg.wadzack@fu-berlin.de
Waha	Andreas	PD Dr. rer. nat.	University of Bonn	awaha@uni-bonn.de
Walser	Sandra		Max Planck Institute of Psychiatry, München	walser@mpipsykl.mpg.de
Walter	Lutz	Prof. Dr.	German Primate Center, Göttingen	lwalter@gwdg.de
Walter	Joern	Prof. Dr..	Saarland University	j.walter@mx.uni-saarland.de
Wanker	Erich	Prof. Dr.	Max-Delbrück-Centrum Berlin-Buch	ewanker@mdc-berlin.de
Warnatz	Hans-Jörg	Dr.	Max Planck Institute for Molecular Genetics, Berlin	warnatz@molgen.mpg.de
Weber	Yvonne	PD Dr. med.	University of Tuebingen	yvonne.weber@uni-tuebingen.de
Weidinger	Stephan	Prof. Dr. med.	University Kiel	sweidinger@dermatology.uni-kiel.de
Weis	Tanja	Dr.	Heidelberg University	tanja.weis@med.uni-heidelberg.de
Weller	Andreas	Dr.	PT-DLR, Bonn	andreas.weller@dlr.de
Werner	Mario		Affymetrix	mario_werner@affymetrix.com
Wichmann	Christian	MD	Georg-Speyer-Haus, Frankfurt am Main	c.wichmann@em.uni-frankfurt.de
Wieland	Thomas		Helmholtz Zentrum München	thomas.wieland@helmholtz-muenchen.de
Wiemann	Stefan	PD Dr.	Deutsches Krebsforschungs-zentrum, Heidelberg	s.wiemann@dkfz.de
Wierling	Christoph	Dr	MPI for Molecular Genetics, Berlin	wierling@molgen.mpg.de
Will	Hans	Prof. Dr.	Heinrich-Pette Institute, Hamburg	hans.will@hpi.uni-hamburg.de

Surname	First name	Title	Institution	Email
Williams	Julie	Prof	Cardiff University School of Medicine, UK	WilliamsJ@cf.ac.uk
Witten	Anika	Dr.	Leibniz-Institute for Arteriosclerosis Research, Münster	anika.sietmann@lifa-muenster.de
Wittig	Michael		Christian-Albrechts-Universität, Kiel	m.wittig@mucosa.de
Wolf	Stephan	Dr. rer. nat.	German Cancer Research Center, Heidelberg	s.wolf@dkfz.de
Wolfrum	Katharina		Max Planck Institute for Molecular Genetics, Berlin	wolfrum@molgen.mpg.de
Wunderlich	Andrea		Max Planck Institute for Molecular Genetics, Berlin	wunder_a@molgen.mpg.de
Wurst	Wolfgang	Prof. Dr.	Helmholtz Zentrum München	wurst@helmholtz-muenchen.de
Yaspo	Marie-Laure	Dr	Max Planck Institute for Molecular Genetics, Berlin	yaspo@molgen.mpg.de
Zapatka	Marc	Dr	German Cancer Research Center, Heidelberg	m.zapatka@dkfz.de
Zazzu	Valeria	PhD	Max Planck Institiue for Molecular Genetics, Berlin	zazzu@molgen.mpg.de
Zell	Andreas	Prof. Dr.	Univ. Tübingen	andreas.zell@uni-tuebingen.de
Zeller	Tanja	Dr.	Medical University Hamburg	t.zeller@uke.de
Zickmann	Franziska		Robert Koch-Institut, Berlin	zickmannF@rki.de
Zimmer	Ralf	Prof. Dr.	LMU München	zimmer@ifi.lmu.de
Zimmermann	Wolfgang	Dr.	LGC Genomics	wolfgang.zimmermann@lgcgenomics.com
Zimmermann	Karin		Humboldt University, Berlin	zimmer@informatik.hu-berlin.de
Zollbrecht	Christa		Universitätsklinikum Regensburg	christa.zollbrecht@klinik.uni-regensburg.de
Zouhair	Aherrahrou	Dr.	Universität zu Lübeck	zouhair.aherrahrou@uk-sh.de

List of NGFN-Plus Integrated Genome Research Networks and NGFN-Transfer Innovation Alliances

IG Atherogenomics

Koordination: Prof. Dr. Heribert Schunkert

Projektleiter				Teilprojekt
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**
Schunkert	Heribert	Prof. Dr. med.	Universität zu Lübeck	A1a, A2a, E1, F1
Erdmann	Jeanette	Prof. Dr. rer. nat.	Universität zu Lübeck	A1a, A2a C2, F1
Diemert	Patrick	PD Dr. med.	Universität zu Lübeck	A2a, D1, D2a
Aherrarhou	Zouhair	Dr. med.	Universität zu Lübeck	B2
Ehlers	Eva-Maria	PD Dr. med.	Universität zu Lübeck	B2
Döhring	Lars	Dr. med.	Universität zu Lübeck	B2
Fischer	Marcus	PD. Dr. med.	Universität zu Regensburg	A2b, D2b
Hengstenberg	Christian	Prof. Dr. med.	Universität zu Regensburg	A1b, C1, E1
Teupser	Daniel	PD Dr. med.	Universität Leipzig	B1
Thiery	Joachim	Prof. Dr. med.	Universität Leipzig	B1
Blankenberg	Stefan	Prof. Dr. med.	Klinikum der Johannes Gutenberg-Universität Mainz	A3a, D1, E1
Zeller	Tanja	Dr. rer. nat.	Klinikum der Johannes Gutenberg-Universität Mainz	A3a, D1, E1
Steller	Ulf	Dr. rer. nat.	Euroimmun AG	E1
Koenig	Wolfgang	Prof. Dr. med.	Universitätsklinikum Ulm	A3b, C1, E2
König	Inke	PD Dr. rer. nat.	Universität zu Lübeck	C2b
Wichmann	H. Erich	Prof. Dr. rer. nat. Dr. med.	Helmholtz Zentrum München	C1
Ziegler	Andreas	Prof. Dr. rer. nat.	Universität zu Lübeck	C2b
Meitinger	Thomas	Prof. Dr. med.	Helmholtz Zentrum München	CF

Erklärung

A. Explorative Genomics

A1 Polygenic and monogenic forms of MI

A2 Genomics of coronary artery disease

A3 Genomics of sub clinical atherosclerosis

B. Comparative Genomics

B1 Syntenic regions for atherosclerosis in mice and humans

B2 ABCC6 and arterial calcification

C. Population Genetics

C1 Cases and population platform (KORA/MONICA; GMIS;PREVENT-IT, LE HEART)

C2 Genetic epidemiology methods platform

D. Functional Genomics

D1 Gene expression profiling Transcriptome of monocytes in subclinical atherosclerosis and MI patients

D2 Genomics of plasma lipids

E. Transfer

E1 SNP array for atherosclerosis Development of innovative diagnostics

E2 50 K Vascular Disease SNP Array

F. Organisation

F1 Coordinating office

CF Genotyping/sequencing facility

IG Genetics of Heart Failure (Genetik der Herzinsuffizienz)

Koordination: Prof. Dr. Hugo A. Katus

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Katus	Hugo A.	Prof. Dr.	Universitätsklinikum Heidelberg	1a	Genetic Risk of Heart Failure and its Subphenotypes
Hasenfuß	Gerd	Prof. Dr.	Georg-August-Universität Göttingen	1b	Genetic Risk of Heart Failure and its Subphenotypes
Kääb	Stefan	Prof. Dr.	Ludwig-Maximilians-Universität München	1c	Genetic Risk of Heart Failure and its Subphenotypes

Kreutz	Reinhold	Prof. Dr.	Charité 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	PD Dr.	Universitätsklinikum Heidelberg	4	Genetic Modifiers of Heart Failure in Mice
Rottbauer	Wolfgang	Prof. 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
Guan	Kaomei	Dr.	Georg-August-Universität Göttingen	7	Genetics and Functional Analysis of Cardiac Mechanosensation - Relevance for the Pathophysiology of Diastolic Heart Failure
Lehnart	Stephan	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 Arterioskleroseforschung an der Universität Münster	10	Genetic epidemiology of Heart Failure: Genetic Epidemio-logical Support for the IG
Eils	Roland	Prof. Dr.	Deutsches Krebsforschungszentrum	11	Bioinformatic Methods
Brors	Benedikt	Dr.	Deutsches Krebsforschungszentrum	11	Bioinformatic Methods
Katus	Hugo A.	Prof. Dr.	Universitätsklinikum Heidelberg	12	DNA-Platform
Meder	Benjamin	Dr.	Universitätsklinikum Heidelberg	12	DNA-Platform
Rottbauer	Wolfgang	Prof. Dr.	Universitätsklinikum Heidelberg	13	High-throughput functional in vivo evaluation of heart failure associated genes and pathways by Morpholino knock-down in zebrafish
IG Molekulare Mechanismen der Adipositas Koordination: Prof. Dr. Johannes Hebebrand					
Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Hinney	Anke	PD Dr.	Universität Duisburg-Essen	TP1	Identification of human obesity genes with a focus on developmental aspects
Schürmann	Annette	Prof. Dr.	Deutsches Institut für Ernährungsforschung (DIfE)	TP2	Identification and characterization of obesity genes, gene-gene and diet gene interactions involved in polygenic obesity in mice
Klingenspor	Martin	Prof. Dr.	Technische Universität München	TP3a	Alterations of the mouse brain proteome associated with the early development of diet-induced obesity in the mouse

Stühler	Kai	PD Dr.	Ruhr-Universität Bochum	TP3b	Alterations of the mouse brain proteome associated with the early development of diet-induced obesity in the mouse
Illig	Thomas	Prof. Dr.	Helmholtz Zentrum München Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH)	WB2-Aa	Evaluation of candidate genes for obesity and related disorders in large representative epidemiological cohorts encompassing children and adults - KORA
Reinehr	Thomas	PD Dr.	Institut für Pädiatrische Ernährungsmedizin, Vestische Kinder- und Jugendklinik, Universität Witten/Herdecke	WB2-Ab	Evaluation of candidate genes for obesity and related disorders in large representative epidemiological cohorts encompassing children and adults - Obeldicks
Krude	Heiko	Prof. Dr.	Charité	WB2-B	WB2-BEPOC
Moebus	Susanne	PD Dr.	Universität Duisburg-Essen	WB2-C	WB2-RECALL
Wabitsch	Martin	Prof. Dr.	Universität Ulm	WB2-D	WB2-UPOC
Rosskopf	Dieter	Prof. Dr.	Universität Greifswald	WB2-E	WB2-SHIP
Boeing	Heiner	Prof. Dr.	Deutsches Institut für Ernährungsforschung (DIfE)	WB2-F	WB2-EPIC
Klingenspor	Martin	Prof.Dr.	Technische Universität München	WB3-Aa	Novel mouse models for the evaluation of candidate genes in the physiology of energy balance regulation
Wurst	Wolfgang	Prof. Dr.	Helmholtz Zentrum München Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH)	WB3-Ab	Novel mouse models for the evaluation of candidate genes in the physiology of energy balance regulation
Fischer-Posovszky	Pamela	Dr.	Universität Ulm	WB3-B	Adipogenese
Horsthemke	Bernhard	Prof. Dr.	Universität Duisburg-Essen	WB3-C	Allelische Expression
Biebermann	Heike	PD Dr.	Charité	WB3-C	Methylierung
Brockmann	Gudrun	Prof. Dr.	Humboldt-Universität zu Berlin	WB3-D	Bioinformatik
Rüther	Ulrich	Prof. Dr.	Heinrich-Heine-Universität Düsseldorf	TP10	Investigation of Fto as a major contributor to obesity
Sauer	Sascha	Dr.	Max-Planck-Institut für Molekulare Genetik (MPIMG)	TP11a	Systematic molecular characterisation of compounds for prevention and therapy of obesity and insulin resistance
Büssow	Konrad	Dr	HZI Braunschweig	TP11b	Systematic molecular characterisation of compounds for prevention and therapy of obesity and insulin resistance
Blüher	Matthias	Prof. Dr.	Universität Leipzig	TP12	Adverse effects of weight cycling on longevity in rodents
Brockmann	Gudrun	Prof. Dr.	Humboldt-Universität zu Berlin	TP14	Implications of diet and exercise with interaction of allelic variations in the Berlin Fat Mouse line
Schäfer	Helmut	Prof. Dr.	Philipps-Universität Marburg	TP15a	Central statistical genomics and data management
Scherag	André	Dr.	Universität Duisburg-Essen	TP15b	Central statistical genomics and data management
Hebebrand	Johannes	Prof. Dr.	Universität Duisburg-Essen	TP16	Coordination and quality management

IG Pathogenic role of mi-RNA in Herpes Infections

Koordination: Prof. Dr. Dr. Jürgen G. Haas

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Haas	Jürgen G.	Prof. Dr. Dr.	LMU , München	1	Herpesviral factors modulating the cellular miRNA processing machinery
Koszinowski	Ulrich	Prof. Dr.	LMU	2	Characterization of CMV miRNAs in vitro and in vivo
Dölken	Lars	Dr.	LMU	2	Characterization of CMV miRNAs in vitro and in vivo
Adler	Heiko	Prof. Dr.	Helmholtz-Zentrum München	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	Prof. Dr.	Universität Regensburg	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

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Reinhardt	Richard	Dr.	MPI für Molekulare. Genetik	1	Ultra-High-Parallel Sequencing and Biocomputational Analysis of npcRNA
Vogel	Jörg	Prof. Dr.	Julius-Maximilians-Universität Würzburg	2a	RNomics of bacterial infections
Rudel	Thomas	Prof. Dr.	Universität Würzburg	2b	RNomics of bacterial infections
Walter	Lutz	Prof. Dr.	Deutsches Primatenzentrum Göttingen	3	RNomics of viral infections
Brosius	Jürgen	Prof. Dr.	Universität Münster	4	RNomics of eukaryotic parasites

IG Systematic Genomics of Chronic Inflammatory Barrier Diseases

Koordination: Prof. Dr. Stefan Schreiber

Projektleiter				Teilprojekt	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
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	Prof. 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	Prof. 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
Rosenstiel	Philip	Prof. Dr.	Uniklinik Schleswig-Holstein, Campus Kiel	GP 9	Funktionelle Aufklärung
Platzer	Matthias	Prof. Dr.	FLI- Leibniz-Institut für Altersforschung	GP 9	Funktionelle Aufklärung
Rosenstiel	Philip	Prof. Dr.	Uniklinik Schleswig-Holstein, Campus Kiel	GP 10	Systematische Aufklärung von Signaltransduktions-wegen: angeborene Immunität
Rüther	Andreas	Dr.	Uniklinik Schleswig-Holstein, Campus Kiel	T1	Qualitätsmanagement
Wittig	Michael		Uniklinik Schleswig-Holstein, Campus Kiel	T3a	Bioinformatische Unterstützung
Jacobs	Gunnar	Dr.	Uniklinik Schleswig-Holstein, Campus Kiel	T5a	Hochdurchsatz zelluläre Screening Assays via RNA Interferenz
Krawczak	Michael	Prof. Dr.	Uniklinik Schleswig-Holstein, Campus Kiel	T2	Genetisch-epidemiologische Unterstützung
Nothnagel	Michael	Dr.	Uniklinik Schleswig-Holstein, Campus Kiel	T2	Genetisch-epidemiologische Unterstützung
Kabesch	Michael	Prof. Dr.	Medizinische Hochschule Hannover	GP 2	Genetische Ätiologie des Asthma bronchiale
Horstmann	Rolf	Prof. Dr.	Bernhard-Nocht-Institut für Tropenmedizin	GP 4	Genetischer Ätiologie der Tuberkulose
Meyer	Christian	Prof. Dr.	Bernhard-Nocht-Institut für Tropenmedizin	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 3b	Bioinformatische Unterstützung
Albrecht	Mario	Dr.	Max Planck Institut für Informatik (MPI-INF)	T 3c	Bioinformatische Unterstützung
Weidinger	Stefan	PD Dr.	Technische Universität München, Klinikum rechts der Isar	GP 5	Genetische Ätiologie der atopischen Dermatitis
Kaufmann	Stefan H.E.	Prof. Dr. Dr. h.c.	Max Planck Institut für Infektionsbiologie	GP11	Systematische Aufklärung von Stoffwechelwegen: Adaptive Immunität
Wiemann	Stefan	PD Dr.	Deutsches Krebsforschungszentrum - DKFZ	T5b	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.**	**Titel**
Döhner	Hartmut	Prof. Dr.	Uni Ulm	TP1	Pathogenecity in AML
Thiede	Christian	Prof. Dr.	TU Dresden	TP2	Novel abnormalities in AML with normal karyotype
Hubert	Serve	Prof. Dr.	Uni Frankfurt	TP3a	Epigenetics of AML
Müller-Tidow	Carsten	Prof. Dr.	Uni Münster	TP3b	Epigenetics of AML

Kulozik	Andreas	Prof. Dr.	Uni Heidelberg	TP4	NOTCH1 signaling
Marschalek	Rolf	Prof. Dr.	Uni Frankfurt	TP5	MLL and stem cell program
Bohlander	Stefan	Prof. Dr.	LMU München	TP6	CALM/AF10 target gene analysis
Feuring-Buske	Michaela	PD. Dr.	Universität Ulm	TP7	MEIS1 homeobox gene expression
Leutz	Achim	Prof. Dr.	MDC Berlin	TP8	Wnt signaling in leukemic stem cells
Duyster	Justus	Prof. Dr.	TU München	TP9	Genetic basis of imatinib resistance
Grez	Manuel	Prof. Dr.	GSH Frankfurt	TP10	Molecular inhibitors of AML1/ETO
Neubauer	Andreas	Prof. Dr.	Uni Marburg	TP11	Resistance to retinoic acid in AML
Schrappe	Martin	Prof. Dr.	Uni Kiel	TP12	Very high risk childhood ALL
Lottaz	Claudio	Dr.	Uni Regensburg	TP13	Bioinformatics, clinical data, and leukemic cell banks
Karawajew	Leonid	Dr.	Charité	TP15	Molecular dissection, functional evaluation and preclinical targeting of intermediate-risk childhood acute lymphoblastic leukemia
Hagemeier	Christian	Prof. Dr.	Charité	TP14 TP16	Systematic approaches towards genes with pathogenetic, prognostic and therapeutic value in relapsed acute lymphoblastic leukemia in children

IG Brain Tumor Network

Koordination: Prof. Dr. Peter Lichter

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**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	Prof. 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
Lichter	Peter	Prof. 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	PD 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	PD 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	Prof. 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-14	Klonierung und funktionelle Charakterisierung des murinen Regenerations- und Toleranz-Faktors: ein Glioma-Autoantigen-Kandidat mit immuno-suppressiven Eigenschaften

IG Integrated Genome Network of Prostate Cancer

Koordination: PD Dr. Holger Sültmann

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Schlomm	Thorsten	PD Dr. med.	Martini-Klinik Prostatakrebszentrum und UKE Hamburg	TP1	Kollektivierung und Bereitstellung von klinischen Proben und Patientendaten
Simon	Ronald	PD Dr.	UKE Hamburg-Eppendorf	TP2	Biologische und klinische Signifikanz von Mikroamplifikationen im Prostatakarzinom
Yekebas	Emre	Prof. Dr.	UKE Hamburg-Eppendorf	TP3	Zytogenetische und molekulare Charakterisierung von Translokations-Bruchpunkten im Prostatakarzinom
Dierlamm	Judith	Prof. Dr. Dr.	UKE Hamburg-Eppendorf	TP3	Zytogenetische und molekulare Charakterisierung von Translokations-Bruchpunkten im Prostatakarzinom
Schweiger	Michal-Ruth	Dr. Dr.	MPI für Molekulare Genetik	TP4	Analyse von Mutationen und epigenetischen Veränderungen im Prostatakarzinom
Lehrach	Hans	Prof. Dr.	MPI für Molekulare Genetik	TP4	Analyse von Mutationen und epigenetischen Veränderungen im Prostatakarzinom
Sültmann	Holger	PD Dr.	Deutsches Krebsforschungszentrum	TP5	Splice-Varianten- und miRNA Expression in Tumoren
Kuner	Ruprecht	Dr.	Deutsches Krebsforschungszentrum	TP5	Splice-Varianten- und miRNA Expression in Tumoren
Balabanov	Stefan	Dr. rer. nat. Dr. med.	Universitätsklinikum Hamburg Eppendorf	TP6	Identifizierung klinisch relevanter Proteine im Prostatakarzinom
Heitmann	Alke	Dr.	Qiagen Hamburg GmbH	TP7	Entwicklung und Kommerzialisierung eines diagnostisch einsetzbaren Tools zur Detektion molekularer Marker im Prostatakarzinom
Haese	Alexander	PD Dr.	Martini-Klinik Prostatakrebszentrum und UKE Hamburg	TP8	Identifizierung und Validierung von diagnostischen und prognostischen Markern für die Therapieentscheidung beim Prostatakarzinom
Korf	Ulrike	Dr.	Deutsches Krebsforschungszentrum	TP9	Proteinarrays zur quantitativen Analyse von Proteinen in Tumoren und in Patientenseren
Weller	Horst	Prof. Dr.	Centrum für Angewandte Nanotechnologie (CAN) GmbH	TP10	Molekulare Tumor-Bildgebung mit Hilfe Antikörper-gekoppelter Nanopartikel
Mollenhauer	Jan	Prof. Dr.	Deutsches Krebsforschungszentrum	TP11	Funktionelle zelluläre Assays in Prostatakarzinom-Zelllinien

Sültmann	Holger	PD Dr.	Deutsches Krebsforschungszentrum	TP12	In vivo Analyse von Genen im Prostatakarzinom
Beissbarth	Tim	Prof. Dr.	Deutsches Krebsforschungszentrum	TP13	Bioinformatik und Systembiologie
Sültmann	Holger	PD Dr.	Deutsches Krebsforschungszentrum	TP14	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.**	**Titel**
Berthold	Frank	Prof. Dr.	Klinikum der Universität zu Köln, Zentrum für Kinderheilkunde und Jugendmedizin	2a	Central database & tumorbank
				8	Predictive gene signatures and transcription 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
Eggert	Angelika	Prof. Dr.	Universitäts-Kinderklinik Essen	4a	Proteomics of NB master regulators
Eggert	Angelika	Prof. Dr.	Universitäts-Kinderklinik Essen	9a	NB Toponome
Eilers	Martin	Prof. Dr.	Philipps-Universität Marburg	11	Systematic drug testing
Fischer	Matthias	PD 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	5a	Identification of NB initiating genes
König	Rainer	PD Dr.	Institut für Pharmazie und Molekulare Biotechnologie/Bioquant	12	Refined treatment selection with machine learning techniques
Lawerenz	Christian	Dr.	Deutsches Krebsforschungszentrum	2b	Central database & tumorbank
Lode	Holger	Prof. Dr.	Charité Campus Virchow-Klinikum	15	Genetic vaccination
Oberthür	André	Dr.	Zentrum für Kinderheilkunde	9b	NB Toponome
Savelyeva	Larissa	Dr.	Deutsches Krebsforschungszentrum	10	NB Fragilome
Schramm	Alexander	PD Dr.	Universitäts-Kinderklinik Essen	4a	Proteomics of NB master regulators
				6	Role of microRNAs in NB pathogenesis
Schubert	Walter	Dr.	Otto-von-Guericke-Universität Magdeburg	9c	NB Toponome
Schulte	Johannes H.	Dr.	Universitäts-Kinderklinik Essen	5b	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	Prof. Dr.	Ruhr-Universität Bochum	4b	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: PD Dr. Roman Thomas

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Thomas	Roman	Dr.	Max-Planck-Institute	0	Coordinating office
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	4	Functional impact of oncogene mutants and small molecules on the Ras and Rho signaling pathways
Wittinghofer	Alfred	Prof. Dr.	MPI für molekulare Physiologie	4	Functional impact of oncogene mutants and small molecules on the Ras and Rho signaling pathways
Rauh	Daniel	Prof. Dr.	MPI for Molecular Physiology Dortmund	5	Dissection of oncogene dependencies by small organic molecule perturbations
Waldmann	Herbert	Prof. Dr.	MPI for Molecular Physiology Dortmund	5	Dissection of oncogene dependencies by small organic molecule perturbations
Rahnenführer	Jörg	Prof. Dr.	University Dortmund	6b	Statistical modeling of drug response and pathway alterations
Lengauer	Thomas	Prof. Dr. Dr.	MPI für Informatik	6a	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.**	**Titel**
Lange	Bodo	PD Dr.	Max-Planck-Institut für Molekulare Genetik	TP1	Project coordination
Lehrach	Hans	Prof. Dr.	Max-Planck-Institut für Molekulare Genetik	TP1	Project coordination
Brand	Angela	Prof. Dr.	Maastricht University	TP2	Translational Health Research
Schulte in den Bäumen	Tobias	Dr.	Maastricht University	TP2	Translational Health Research
Schweiger	Michal-Ruth	Dr. Dr.	Max-Planck-Institut für Molekulare Genetik	TP3	Mutational analysis
Mollenhauer	Jan	Prof. Dr.	Medical Biotechnology Center University of Southern Denmark	TP4	Recombinant cancer cell libraries & drug target recovery

Sültmann	Holger	PD Dr.	German Cancer Research Center (DKFZ)	TP5	Quantification of cancer pathways
Wanker	Erich	Prof. Dr.	Max-Delbrück-Centrum für Molekulare Medizin	TP6	Protein interaction networks
Schäfer	Reinhold	Prof. Dr.	Charité Universitätsmedizin Berlin	TP7	Cellular signalling networks
Herrmann	Bernhard	Prof. Dr,	Max-Planck-Institut für Molekulare Genetik	TP8	Mouse disease models
Morkel	Markus	Dr.	Max-Planck-Institut für Molekulare Genetik	TP8	Mouse disease models
Lange	Bodo	PD Dr.	Max-Planck-Institut für Molekulare Genetik	TP9	Protein complex composition and function in disease
Wierling	Christoph	Dr.	Max-Planck-Institut für Molekulare Genetik	TP10	Data integration and modelling
Drewes	Gerard	PD Dr.	Cellzome AG	TP11	Quantitative Proteomics
Joberty	Gerard	Dr.	Cellzome AG	TP11	Quantitative Proteomics

IG Translational Genome Research Network in Pancreatic Cancer

Koordination: Prof. Dr. Thomas M. Gress

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Gress	Thomas M.	Prof. Dr.	Philipps-Universität Marburg	TP0,TP1b, TP2b,	TP0 Koordination TP1b Klinische Ressourcen und Daten TP2b Mausmodelle des Pankreaskarzinoms
Buchholz	Esther		Philipps-Universität Marburg	TP 0	TP 0 Koordination
Giese	Nathalia	Dr.	Universitätsklinikum Heidelberg	TP1a	Klinische Ressourcen und Daten
Tannapfel	Andrea	Prof. Dr.	Ruhr-Universität Bochum	TP1c	Klinische Ressourcen und Daten
Sipos	Bence	Prof. Dr.	Eberhard-Karls Universität Tübingen	TP1d	Klinische Ressourcen und Daten
Sipos	Bence	Prof. Dr.	Eberhard-Karls Universität Tübingen	TP2c	Mausmodelle des Pankreaskarzinoms
Schmid	Roland M.	Prof. Dr.	TU München	TP2a	Mausmodelle des Pankreaskarzinoms
Buchholz	Malte	PD Dr.	Philipps-Universität Marburg	TP3, TP11a	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	TP6	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	TP9a	Entwicklung von molekulardiagnostischen Verfahren zur Früherkennung des Pankreaskarzinoms basierend auf sezernierten/freigesetzten Kandidaten-Proteinen
Schnölzer	Martina	Dr.	DKFZ Heidelberg	TP9b	Entwicklung von molekulardiagnostischen Verfahren zur Früherkennung des Pankreaskarzinoms basierend auf sezernierten/freigesetzten Kandidaten-Proteinen
Kestler	Hans	Prof. Dr.	Uniklinik Ulm	TP11b	Molekulare Differentialdiagnose
Günther	Simone	Dr.	Applied Biosystems	TP11c	Molekulare Differentialdiagnose

IG Modifiers of Intestinal Tumor Formation and Progression
Koordination: Prof. Dr. Bernhard Herrmann

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Schweiger	Michal-Ruth	Dr. 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.**	**Titel**
Hampe	Jochen	PD Dr.	Universitätsklinikum Schleswig-Holstein	TP1	Fine mapping + replication
Hemminki	Kari	Prof. Dr.	Deutsches Krebsforschungszentrum	TP2	Population-based studies
Schafmayer	Clemens	Dr.	Universitätsklinikum Schleswig-Holstein	TP2	Population-based and prospective validation

Chang-Claude	Jenny	Prof. Dr.	Deutsches Krebsforschungszentrum	TP2	Population-based and prospective validation
Brenner	Hermann	Prof. Dr.	Deutsches Krebsforschungszentrum	TP2	Population-based and prospective validation
Burwinkel	Barbara	Prof. Dr.	Deutsches Krebsforschungszentrum	TP2	Population-based and prospective validation
Krawczak	Michael	Prof. Dr.	Universitätsklinikum Schleswig-Holstein	TP3	Statistics and Genetic epidemiology
Brosch	Mario	Dr.	Universitätsklinikum Schleswig-Holstein	TP4	Somatic mutation signature
Platzer	Matthias	Prof. Dr.	Leibniz-Institut für Altersforschung	TP4	Somatic mutation signature
Siebert	Reiner	Prof. Dr.	Universitätsklinikum Schleswig-Holstein	TP5	Somatic genomic imbalances, LOH and methylation
Boutros	Michael	Prof. Dr.	Deutsches Krebsforschungszentrum	TP6	Systems biology of signaling pathways in colorectal carcinomas
Spang	Rainer	Prof. Dr.	Universität Regensburg	TP7	System biology of the cancer cell
Kalthoff	Holger	Prof. Dr.	Universitätsklinikum Schleswig-Holstein	TP8	Pathways: tumor tissue
Hemminki	Kari	Prof. Dr.	Deutsches Krebsforschungszentrum	TP9	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.**	**Titel**
Cichon	Sven	Prof. Dr. rer. nat.	Universitätsklinikum Bonn	1	Genomik bei Bipolarer Störung
Schumacher	Johannes	PD Dr.	National Institute of Mental Health (NIMH)	1	Genomik bei Bipolarer Störung
Holsboer	Florian	Prof. Dr. Dr.	Max Planck Institut für Psychiatrie	2	Genomik bei unipolarer Störung
Lucae	Susanne	Dr. Dr.	Max Planck Institut für Psychiatrie	2	Genomik bei unipolarer Störung
Rujescu	Dan	Prof. Dr.	Psychiatrische Klinik der LMU	3	Genomik bei Schizophrenie
Maier	Wolfgang	Prof. Dr.	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.	Zentralinstitut für Seelische Gesundheit	6a	Imaging Genetik
Walter	Henrik	Prof. Dr. med. Dr. phil.	Universitätsmedizin Charite, Campus Mitte	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	Prof. Dr. rer. nat.	Universitätsklinikum Bonn	9	Allel-spezifische Expression
Becker	Albert	Prof. Dr. med.	Universitätsklinikum Bonn	9	Allel-spezifische Expression
Eils	Roland	Prof. Dr.	DKFZ Heidelberg	10	Methodenentwicklung für biologische Pathway-Informationen in GWA-Analysen
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
Deussing	Jan	Dr.	Max Planck Institute of Psychiatry	12b	Funktionelle Untersuchungen mit Hilfe von transgenen Mausmodellen und Proteomanalysen
Turck	Chris	Prof. Dr. rer. nat.	Max Planck Institut für Psychiatrie	12	Funktionelle Untersuchungen mit Hilfe von transgenen Mausmodellen und Proteomanalysen
Nöthen	Markus	Prof. Dr. med.	Universitätsklinikum Bonn	14	Projekt-Management und Graduierten-Training
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.**	**Titel**
Spanagel	Rainer	Prof. Dr.	Central Institute of Mental Health	1	Coordination Consortium
Eils	Roland	Prof. Dr.	German Cancer Research Center	2a	Gene data mining platform and statistics
Brors	Benedikt	Dr.	German Cancer Research Center	2a	siehe Eils
Wienker	Thomas	Prof. Dr.	University of Bonn	2b	siehe Eils
Matthäus	Franziska	Dr.	University of Heidelberg,	3	Mathematical Modelling and Analysis
Jäger	Willi	Prof. Dr. Dr. h.c. mult	University of Heidelberg,	3	siehe Matthäus
Schütz	Günter	Prof. Dr. med.	German Cancer Research Center (DKFZ)	4	Functional analysis I and conditional mouse models
Wurst	Wolfgang	Prof. Dr.	GSF - National Research Center for Environment and Health	5	Functional analysis II and RNAi in vivo application
Deussing	Jan	Dr.	Max Planck Institute of Psychiatry	5	siehe Wurst

Zimmer	Andreas	Prof. Dr.	University of Bonn	6	Functional analysis III
Bartsch	Dusan	Prof. Dr.	Central Institute of Mental Health	7	Transgenic rat models
Zimmer	Andreas	Prof. Dr.	University of Bonn	8	Behavioral analysis of Animal Models
Spanagel	Rainer	Prof. Dr.	Central Institute of Mental Health	8	Behavioral analysis of Animal Models
Gebicke-Haerter	Peter	Prof. Dr.	Central Institute of Mental Health	9	Glutamatergic and epigenetic profiling with microarrays
Hoheisel	Jörg	Dr.	Deutsches Krebsforschungszentrum	9	siehe Gebicke-Haerter
Sprengel	Rolf	Dr.	MPI Med. Forschung Heidelberg	10	Transcriptional and posttranscriptional modifications
Rietschel	Marcella	Prof. Dr.	Central Institute of Mental Health	11	GWA studies in alcohol dependent patients and replication studies
Nöthen	Markus	Prof. Dr.	University of Bonn	11	siehe Rietschel
Dahmen	Norbert	PD Dr.	Universität Mainz	12a	GWA studies in population-based samples for high versus low alcohol consumption and replication studies
Wichmann	H. Erich	Prof. Dr.	GSF Institute of Epidemiology	12b	siehe Dahmen
Heinz	Andreas	Prof. Dr.	University Medical Center Berlin, Campus Charité	13b	Endophenotyping with fMRI: Genetic modulation and treatment response
Walter	Henrik	Prof. Dr.	Universitaetsmedizin Charite, Campus Mitte	13a	siehe Heinz
Kiefer	Falk	Prof. Dr.	Central Institute of Mental Health	13c	siehe Heinz
Mann	Karl	Prof. Dr. Dr.	Central Institute of Mental Health	14a	Endophenotyping with spectroscopy: Genetic modulation and treatment response
Ende	Gabriele	Dr.	Central Institute of Mental Health	14a	siehe Mann
Gallinat	Jürgen	Prof. Dr.	Psychiatry, Charité, CCM	14b	siehe Mann
Sartorius	Alexander	Prof. apl.	Central Institute of Mental Health	15	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.**	**Titel**
Reis	André	Prof. 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 Forschungszentrum 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	Prof. 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.**	**Titel**
Kubisch	Christian	Prof. Dr.	University of Ulm	1	Genome-wide association analysis and gene identification in migraine with aura
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. med. habil.	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	Prof. Dr.	University of Bonn	5	Genetic basis of Levetiracetam pharmacoresistance and side effects in human epilepsy (TP5)
Lerche	Holger	Prof. Dr.	Universitätsklinikum Tübingen	6	Functional analysis of human ion channel mutations in cellular and animal models (TP6)
Becker	Albert	Prof. Dr.	University of Bonn	7	Aberrant transcriptional networks in human epileptic tissue
Beck	Heinz	Prof. Dr.	University of Bonn	8	Mechanisms underlying the development of cellular hyperexcitability in mouse models of human epilepsy
Isbrandt	Dirk	Prof. Dr.	University of Hamburg	9	Subthreshold ion channels in epileptogenesis and neuronal synchronization

IG Gene Identification and Functional analyses in Alzheimer's disease Koordination: Prof. Dr. Matthias Riemenschneider					
Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Riemenschneider	Matthias	Prof. Dr	Universitätsklinikum des Saarlandes	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 (Dr. Thomas Floss)	Wolfgang	Prof. Dr.	Helmholtz Zentrum München	9	Animal models for candidate genes of Alzheimer's disease
Riemenschneider	Matthias	Prof. Dr.	Universitätsklinikum des Saarlandes	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.**	**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 α-synuclein-based in vitro model of Parkinson’s disease
Schulz	Jörg B.	Prof. Dr.	Universität Aachen	TP5	Modifier screen in flies overexpressing LRRK2
Zweckstetter	Markus	Prof. Dr.	Max-Planck-Institut für Biophysikalische Chemie	TP6	Molecular mechanisms of pathogenic misfolding of α-synuclein
Auburger	Georg	Prof. Dr.	J.W. Goethe University	TP7	Biomarkers of the common Parkinson pathway:α-Synuclein induction and synaptic pathology in recessive PD

Riess	Olaf	Prof. Dr.	Eberhard-Karls-Universität Tübingen	TP8	Calpain cleavage of α-synuclein in the pathogenesis 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
Haass	Christian	Prof. Dr.	Ludwig-Maximilians-Universität München	TP11	The physiological and pathological function of PINK 1, parkin and LRRK2 in zebrafish and other models
Ueffing	Marius	Prof. Dr.	TU München	TP12	Functional characterization of LRRK2 in mammalian cells and tissues
Roeper	Jochen	Prof. Dr.	J.W. Goethe University	TP13a	Dopaminergic dysfunction and molecular pathways to selective neurodegeneration: from mouse models to Parkinson disease
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
Wurst (Dr. Daniela Vogt-Weisenhorn)	Wolfgang	Prof. Dr.	Helmholtz Zentrum München	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.**	**Titel**
Wanker	Erich	Prof. Dr.	Max-Delbrück-Centrum für Molekulare Medizin	1	Protein-Protein Interaktionsnetzwerke bei neurodegenerativen Erkrankungen

Selbach	Matthias	Prof. 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 Protein-komplexkomposition und Funktion durch Stress und Neurodegenerative Krankheitssignale
Wanker	Erich	Prof. Dr.	Max-Delbrück-Centrum für Molekulare Medizin	6a	Erstellung von Genexpressionssignaturen von neurodegenerativen Krankheitsprozessen
Nietfeld	Wilfried	Dr.	Max-Planck-Institut für Molekulare Genetik	6b	Erstellung von Genexpressionssignaturen von neurodegenerativen Krankheitsprozessen
Bork	Peer	Prof. Dr.	European Molecular Biology Laboratory	6c	Erstellung von Genexpressionssignaturen von neurodegenerativen Krankheitsprozessen
Boutros	Michael	Prof. Dr.	Deutsches Krebsforschungszentrum	7	Systematische Analyse von Phänotypen mittels RNAi und kleinen Molekülen
Bork	Peer	Prof. Dr.	European Molecular Biology Laboratory	8a	Datenintegration und Erstellung von Phänotyp-Protein-Wirkstoff Netzwerken
Andrade	Miguel	Dr.	Max-Delbrück-Centrum für Molekulare Medizin	8b	Datenintegration und Erstellung von Phänotyp-Protein-Wirkstoff Netzwerken
Wanker	Erich	Prof. Dr.	Max-Delbrück-Centrum für Molekulare Medizin	9	Management der IG „NeuroNet“
Wanker	Erich	Prof. Dr.	Max-Delbrück-Centrum für Molekulare Medizin		Wissenschaftliche Plattform „Interaktom“ für systematische Protein-Interaktionsstudien

IG From Disease genes to Protein Pathways (DiGTOP)

Koordination: Prof. Dr. Wolfgang Wurst

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Stewart	Francis	Prof. Dr.	Technische Universität Dresden	1	Genidentifikation und DNA Konstruktproduktion
von Melchner	Harald	Prof. Dr.	Universität Frankfurt	2	In situ Markierung von Krankheitsproteinen in embryonalen Stammzellen mit Genfallen-induzierten Mehrzweckallelen
Wurst (Dr. Joel Schick)	Wolfgang	Prof. Dr.	Helmholtz Zentrum München	3	Produktion proteinmarkierter pluripotenter und differenzierter ES Zellen
Hyman	Tony	Prof. Dr.	MPI für Zellbiologie und Genetik Dresden	4	Produktion und Imaging von HeLa und ES Zelllinien

Brüstle	Oliver	Prof. Dr.	Universität Bonn	5	Etablierung und Analyse transgener hES Zelllinien und neuralen Stammzelllinien
Mann	Matthias	Prof. Dr.	MPI für Biochemie, Martinsried	6	Proteininteraktionsstudien mittels massenspektrometrie-basierter Proteomik in in vitro und in vivo Systemen
Hansen (Prof. Dr. Wurst)	Jens	Dr.	Helmholtz Zentrum München	7a	DiGtoP bioinformatics – resource development and application in comparative network analysis
Gibson	Toby	Prof. Dr.	EMBL Heidelberg	7	DiGtoP bioinformatics – resource development and application in comparative network analysis
Kühn (Prof. Dr. Wurst)	Ralf	Dr.	Helmholtz Zentrum München	8	Mausmodelle für die in vivo Validierung von Proteininteraktionen
Buchholz	Frank	Prof. Dr.	MPI für Zellbiologie und Genetik Dresden	9	Validierung und Zergliederung der Signalwege von Krankheitsrelevanten Genen mit endoribonucelase präparierter siRNA
Wurst (Dr. Michael Miller)	Wolfgang	Prof. Dr.	Helmholtz Zentrum München	10	Management & Training

IG German Mouse Clinic (GMC)

Koordination: Prof. Dr. Martin Hrabě de Angelis

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Hrabě 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. Dr.	Genzentrum der LMU München	2	Clinical Chemical Screen
Wurst	Wolfgang	Prof. Dr.	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. Dr.	Helmholtz Zentrum München	5	Eye Screen
Hrabě de Angelis	Martin	Prof. Dr.	Helmholtz Zentrum München	6	Dysmorphology Screen
Fuchs	Helmut	Dr.	Helmholtz Zentrum München	6	Dysmorphology Screen
Busch	Dirk	Prof. Dr.	TU München	7	Immunology Screen
Ollert	Markus	Prof. Dr.	TU München	8	Allergy Screen
Adamski	Jerzy	Prof. Dr.	Helmholtz Zentrum München	9	Steroid Screen
Zimmer	Andreas	Prof. Dr.	Universitätsklinikum Bonn	10	Nociceptive Screen
Schulz	Holger	Prof. Dr.	Helmholtz Zentrum München	11	Lung Function Screen
Stöger	Tobias	Dr.	Helmholtz Zentrum München	11	Lung Function Screen

Yildirim	Ali Önder	Dr.	Helmholtz Zentrum München	11	Lung Function Screen
Beckers	Johannes	PD Dr.	Helmholtz Zentrum München	12	Molecular Phenotyping Screen
Klingenspor	Martin	Prof. Dr.	TU München	13	Energy Metabolism Screen
Daniel	Hannelore	Prof. Dr.	TU München	13	Energy Metabolism Screen
Katus	Hugo	Prof. Dr.	Universität Heidelberg	14	Cardiovascular Screen
Bekeredjian	Raffi	Dr.	Universität Heidelberg	14	Cardiovascular Screen
Höfler	Heinz	Prof. Dr.	Helmholtz Zentrum München	15	Pathology Screen
Esposito	Irene	Prof. Dr.	Helmholtz Zentrum München	15	Pathology Screen
Hrabě de Angelis	Martin	Prof. Dr.	Helmholtz Zentrum München	16	Data Management
Lengger	Christoph	Dr.	Helmholtz Zentrum München	16	Data Management
Schughart	Klaus	Prof. Dr.	HZI - Helmholtz-Zentrum für Infektionsforschung	17	Host Pathogen Interaction Screen
Hrabě de Angelis	Martin	Prof. Dr.	Helmholtz Zentrum München	18	EMMA
Hagn	Michael	Dr.	Helmholtz Zentrum München	18	EMMA
Hrabě de Angelis	Martin	Prof. Dr.	Helmholtz Zentrum München	01GS0849	Generierung von Mausmodellen

IG MHC Haplotype Sequencing: An Integrated Approach to Common Disease

Koordination: Dr. Margret Hoehe

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Hoehe	Margret	Dr.	MPI-MG Berlin	1	MHC-Haplotypen-Sequenzierung

IG Cellular Systems Genomics in Health and Disease

Koordination: PD Dr. Stefan Wiemann

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Wiemann	Stefan	PD Dr.	DKFZ Heidelberg	1	Projekt Coordination
Körner	Cindy		DKFZ Heidelberg	2	Functional Genomic Resources for NGFNplus
Keklikoglou	Ioanna		DKFZ Heidelberg	3	Cellular Screening Systems
Arlt	Dorit	Dr.	DKFZ Heidelberg	4	Signalling Network analysis
Gavin	Anne-Claude	Dr.	EMBL Heidelberg	5	TAP - Protein interaction mapping
Pepperkok	Rainer	Dr.	EMBL Heidelberg	6	Protein and Network dynamics
Korf	Ulrike	Dr.	DKFZ Heidelberg	7	Quantitative Proteinarrays
Lange	Bodo	PD Dr.	Max-Planck Institut für Molekulare Genetik	8	Primary Cancer Cell Models
Schneeweiss	Andreas	Prof. Dr.	Uniklinik Heidelberg	9	Clinical validation
Beissbarth	Tim	Dr.	DKFZ Heidelberg	10	Pathway reconstruction & modelling

Bender	Christian		DKFZ Heidelberg	11	Integrated bioinformatics
Wiemann	Stefan	PD Dr.	DKFZ Heidelberg	12	QM & Standards
NGFN Geschäftsstelle Koordination: Dr. Silke Argo					
Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Argo	Silke	Dr.	DKFZ Heidelberg	1	Geschäftsstelle des Projektkomitees von NGFN-Plus und NGFN-Transfer im Programm der Medizinischen Genomforschung
KTT Koordination: Dr. Hubert Müller					
Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Müller	Hubert	Dr.	Ascenion GmbH	1	Nationales Genomforschungsnetz: KompetenzCenter Technologietransfer (KTT) – Fortführung
IA Entwicklung prophylaktisch wirksamer Anti-Malaria Verbindungen Koordination: Dr. Birte Sönnichsen					
Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Sönnichsen	Birte	Dr.	Cenix BioScience GmbH	1	Anti Malaria Zielgene und Wirkstoffkandidaten
Matuschewski	Kai	Prof. Dr.	Universität Heidelberg	2	Zielgene im Parasiten
Frischknecht	Friedrich	Dr.	Universität Heidelberg	3	Imaging von Interaktionen des Parasiten mit Leberzellen
IA Breast Cancer Kit Koordination: Prof. Dr. Jan Georg Hengstler					
Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Schmidt	Marcus	Dr. med.	Universität Mainz	1	Chemosensitivity determination, clinical data and tumour tissue banking
Gehrmann	Mathias	Dr.	Siemens Medical Solutions Diagnostic GmbH	2	Identification of gene signatures predicting drug efficacy
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.	Titel
Hecker	Markus	Prof. Dr.	Universität Heidelberg	2	Validierung der Decoy Oligodesoxynukleotid-Medikamentenkandidaten in Herzinsuffizienzmodellen
Wagner	Andreas H.	Priv.-Doz. Dr.	Universität Heidelberg	2	Validierung der Decoy Oligodesoxynukleotid-Medikamentenkandidaten in Herzinsuffizienzmodellen
Müller	Oliver J.	PD Dr. med.	Universität Heidelberg	3	Zellspezifischer Decoy Oligodesoxynukleotid-Transfer ins insuffiziente Herz
Bekeredjian	Raffi	PD Dr. med.	Universität Heidelberg	3	Zellspezifischer Decoy Oligodesoxynukleotid-Transfer ins insuffiziente Herz

IA Metabolomics in Heart Failure as a Novel Diagnostic Tool

Koordination: Prof. Dr. Hugo A. Katus

Projektleiter				Teilprojekt	
Nachname	Vorname	Titel	Institution	Nr.	Titel
Katus	Hugo A.	Prof. Dr.	Universitätsklinikum Heidelberg	1a	Novel Biomarkers for Heart Failure - Metabolic Signatures (Erster Projektleiter und Ansprechpartner auf der Arbeitsebene)
Fuhrmann	Jens	Dr.	metanomics GmbH	1b	Novel Biomarkers for Heart Failure - Metabolic Signatures (Co-Pi und Ansprechpartner auf der Arbeitsebene)
Frey	Norbert	Prof. Dr.	Universitätsklinikum Schleswig-Holstein, Campus Kiel	2	Metabolic Profiling in Mouse Models of Heart Failure (Erster Projektleiter und Ansprechpartner auf der Arbeitsebene)
Müller	Oliver J.	PD Dr.	Universitätsklinikum Heidelberg	2	Metabolic Profiling in Mouse Models of Heart Failure (Co-Pi und Ansprechpartner auf der Arbeitsebene)
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.	Titel
Jankowski	Vera	Dr.	Charité – Universitätsmedizin Berlin	1	Bioanalytik der chronischen Niereninsuffizienz

Nachname	Vorname	Titel	Institution	Nr.	Titel
Jankowski	Joachim	Prof. 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.**	**Titel**
Becker	Karl-Friedrich	Prof. Dr.	Technische Universität München	1	Proteinlysat Mikroarrayanalyse für uPA und PAI-1 von Formalin-fixierten Brustkrebsgeweben
				2	HER2-Rezeptor Expression und Signalwege in Brustkrebsgeweben
Porschewski	Peter	Dr.	Qiagen GmbH	3	Proteomsignaturen in FFPE-Geweben

IA Subgenome Fraktionation for High Throughput Sequencing

Koordination: Dr. med. Benjamin Meder

Projektleiter				**Teilprojekt**	
Nachname	**Vorname**	**Titel**	**Institution**	**Nr.**	**Titel**
Beier	Markus	Dr.	febit AG	1	Development of microarrays for sub-genome preparation
Wiemann	Stefan	PD Dr.	DKFZ	2	Cancer Genome Comparisons
Pfeufer	Arne	PD Dr.	TU München	3a	Cardiomyopathy Re-sequencing
Meder	Benjamin	Dr. med.	Universität Heidelberg	3b	Cardiomyopathy Re-sequencing
Strom	Tim	PD Dr.	Helmholtzzentrum München	4	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.**	**Titel**
Korfhage	Christian	Dr.	Qiagen	1	Development and standardization of new WGA and WTA methods

Wichmann	H.-Erich	Prof. Dr. Dr.	HMGU	2	Provision of biosamples of different quality to test whole genome and transcriptome amplification techniques.
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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