e:Med
SYSTEMS MEDICINE

# e:Med Meeting 2015 on Systems Medicine

October 26 - 28, 2015
DKFZ Heidelberg

e:Med
SYSTEMS MEDICINE

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50 Years – Research for
A Life Without Cancer

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## Welcome Remarks

Dear e:Med colleagues,

The e:Med Project Committee cordially welcomes you at the **e:Med Meeting 2015 on Systems Medicine, October 26 to 28, at DKFZ Heidelberg**.

This meeting is the central e:Med community event for presenting your scientific projects and latest results via talks and posters, discussing novel approaches and establishing new collaborations and partnering in the field of systems medicine. The far reaching implications of the ongoing process to establish the field of systems medicine on the foundation of systems biology are introduced in the **highlight evening lecture** on the first day of the meeting by **Rudi Balling** from the Luxembourg Centre for Systems Biomedicine.

The **main program** is centered on cross-topic subjects as epigenetics & transcriptomics, genome editing, and computational approaches & clinical utilities. In terms of disease entities, the focus is on cardiovascular diseases and cancer as two selected disease topics this year. Other pathologies will be chosen for next year's meeting. Cutting-edge new results will be revealed in the **short talks** sessions with oral presentations selected from the abstracts. These provide the chance to reveal your new work and to discuss scientific issues and techniques with the e:Med community. As modern life sciences raise complex ethical, legal and social aspects (**ELSA**) there is a dedicated "ELSA in systems medicine" session that addresses these issues.

Get an update on the activities of the four **e:Med project groups** on informatics/modelling, epigenetics & sequencing, data security & ethics, and processing of imaging data, visit the presentation on Tuesday afternoon. The **posters** on this year's session topics and as well on neurological disorders, infection & inflammation, and ELSA projects are on display throughout the conference. The **poster session** will attract attention on Tuesday noon. Selected posters will be addressed during guided **poster walks**.

We encourage you to take advantage of the interdisciplinary nature of e:Med conferences to think out of the box of your own work and to get inspired by your colleague's research in another area. To facilitate these interactions each session will start with **keynotes** that introduce the research field covered in the session and that highlight central parts.

Ultimately, don't miss the **networking events** in the evening and meet the e:Med community in a relaxed atmosphere: Monday evening with posters, wine & snacks at the venue and Tuesday evening with dinner in the Heidelberg old town. Here food is offered to you for free, drinks are asked to be paid by each participant. There will be a bus shuttle from the venue to the old town after the main program.

The e:Med networking events are made possible with kind support of our **sponsors**, who will be on site with technical information as well.

We are very much looking forward to welcoming you in Heidelberg!

Lübeck and Heidelberg, October 2015

Professor Dr. Jeanette Erdmann

PD Dr. Karsten Rippe

Speakers of the e:Med project committee

## Scientific Program Committee

**Session I: Epigenetics & Transcriptomics**

PD Dr. Karsten Rippe
Prof. Dr. Christoph Plass
PD Dr. Dirk Hose
Prof. Dr. Philip Rosenstiel

**Session II: Genome Editing**

Prof. Dr. Wolfgang Wurst

**Session III: Cardiovascular Diseases**

Prof. Dr. Jeanette Erdmann
Prof. Dr. Heribert Schunkert
Prof. Dr. Tanja Zeller
Prof. Dr. David Hassel

**Session IV: Computational Approaches & Clinical Utilities**

Prof. Dr. Fabian Theis
PD Dr. Hamid Noori
Dr. Martin Peifer
Prof. Dr. Ingo Röder

**Session V: Cancer**

Prof. Dr. Angelika Eggert
Prof. Dr. Roman Thomas
Prof. Dr. Peter Lichter
Prof. Dr. Hartmut Goldschmidt

**Session VI: Neurological Disorders** (Posters only)

Prof. Dr. Markus Nöthen

**Session VII: Infection and Inflammation** (Posters only)

Prof. Dr. Nina Babel

## Members of the e:Med Project Committee

**Prof. Dr. Jeanette Erdmann**, University of Lübeck

**Prof. Dr. Friedrich Feuerhake**, Hannover Medical School

**Prof. Dr. Hartmut Goldschmidt,** University Hospital Heidelberg

**Prof. Dr. David Hassel**, University Hospital Heidelberg

**Prof. Dr. Steffen Just**, University Hospital Ulm

**Dr. Ulrike Korf,** German Cancer Research Center (DKFZ) Heidelberg

**Prof. Dr. Titus Kühne**, Deutsches Herzzentrum Berlin

**Prof. Dr. Peter Lichter**, German Cancer Research Center (DKFZ) Heidelberg

**Prof. Dr. Markus Nöthen**, University of Bonn

**PD Dr. Karsten Rippe**, German Cancer Research Center (DKFZ) Heidelberg

**Prof. Dr. Ingo Röder**, Technische Universität Dresden

**Prof. Dr. Philip Rosenstiel,** University Hospital Schleswig-Holstein, Kiel

**Dr. Martin Sos**, University Hospital of Cologne

**Prof. Dr. Rainer Spanagel**, Central Institute of Mental Health, Mannheim

**Prof. Dr. Roman Thomas,** University of Cologne

**Prof. Dr. Tanja Zeller**, Universitätsklinikum Hamburg-Eppendorf Hamburg

## Conference Management

**e:Med Management Office**

c/o German Cancer Research Center, DKFZ
Im Neuenheimer Feld 581, V025
D-69120 Heidelberg
Fax: +49 (0)6221 42 46 51

Dr. Silke Argo
E-mail: s.argo@dkfz.de
Phone: +49-6221-424743

Dr. Tanja Jutzi
E-mail: t.jutzi@dkfz.de
Phone: +49-6221-424742

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

## Program

### Monday, October 26, 2015

| | |
|---|---|
| **12:30 - 01:00 pm** | **Registration & Welcome Coffee** |
| **01:00 - 01:15 pm** | **Welcome Notes**<br>**Klaus-Peter Michel** Bundesministerium für Bildung und Forschung (BMBF)<br>**Karsten Rippe** Spokesperson of the e:Med Project Committee |
| **01:15 - 02:45 pm** | **Session I: Epigenetics & Transcriptomics - *Keynotes***<br>Chair: Philip Rosenstiel |
| 01:15 - 01:45 pm | **Karsten Rippe**, DKFZ Heidelberg<br>*Dissecting epigenetic networks* |
| 01:45 - 02:15 pm | **Jörn Walter**, Saarland University<br>*Epigenomics – from mapping to functional interpretation* |
| 02:15 - 02:45 pm | **Dirk Hose**, University Hospital Heidelberg<br>*Transcriptome profiling by RNA-sequencing and its clinical application* |
| **02:45 - 03:15 pm** | **Session I: Epigenetics & Transcriptomics – *Short Talks***<br>Chair: Dirk Hose |
| 02:45 - 03:00 pm | **Berenice Brandt**, University Hospital Schleswig-Holstein<br>*A multi-omics approach to decipher drug specific response signatures in the treatment of IBD* |
| 03:00 - 03:15 pm | **Gaurav Jain**, German Center for Neurodegenerative Diseases<br>*The microRNAome as a biomarker signature for brain diseases* |
| **03:15 - 03:45 pm** | **Coffee Break** |
| **03:45 - 05:45 pm** | **Session II: Genome Editing - *Keynotes***<br>Chair: Wolfgang Wurst |
| 03:45 - 04:15 pm | **Wolfgang Wurst**, Helmholtz Zentrum München<br>*CRISPR/Cas9 Technology: Universal Tool for Functional Genome Annotation* |
| 04:15 - 04:45 pm | **Omar Abudayyeh**, MIT, Harvard, Cambridge, USA<br>*Applications of CRISPR/Cas9 and Discovery of new CRISPR Systems* |
| 04:45 - 05:15 pm | **Darío Jesús García Lupiáñez**, MPI for Molecular Genetics Berlin<br>*CRISVar: Generating structural variations to study the 3D organization of the genome in disease* |
| 05:15 - 05:45 pm | **Hao Yin**, MIT, Harvard, Cambridge, USA<br>*Crispr/Cas9 technology for genome engineering in adult animals: disease modeling and therapeutic application* |
| **05:45 - 06:00 pm** | **Coffee Break** |
| **06:00 - 07:00 pm** | **Evening Lecture**<br>**Rudi Balling**, University of Luxembourg<br>*From Systems Biology to Systems Medicine -An Avalanche is coming-* |
| **07:00 - 10:00 pm** | **Networking** posters, wine & snacks at the venue |

## Tuesday, October 27, 2015

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|---|---|
| **08:30 - 09:00 am** | **Welcome Coffee** |
| **09:00 - 10:30 am** | **Session III: Cardiovascular Diseases - *Keynotes***<br>Chair: Heribert Schunkert |
| 09:00 - 09:30 am | **Jeanette Erdmann**, University of Lübeck<br>*Systems medicine in cardiovascular diseases* |
| 09:30 - 10:00 am | **Sarah Nordmeyer**, Deutsches Herzzentrum Berlin<br>*Systems Medicine of Heart Failure – SMART* |
| 10:00 - 10:30 am | **Johannes Soeding**, MPI for Biophysical Chemistry, Göttingen<br>*Improved prediction of disease-associated SNPs in genome-wide association data by Bayesian modelling and data integration* |
| **10:30 - 11:00 am** | **Coffee Break** |
| **11:00 - 12:30 pm** | **Session III: Cardiovascular Diseases – *Short Talks***<br>Chair: Jeanette Erdmann |
| 11:00 - 11:15 am | **Ingrid Brænne**, University of Lübeck<br>*Analysis of coxibs pleiotropic molecular targets reveals novel genomic loci conferring coronary artery disease risk* |
| 11:15 - 11:30 am | **Helmut Spengler / Thorsten Kessler**, TU München<br>*Data warehouse for coronary artery disease* |
| 11:30 - 11:45 am | **Lingyao Zeng**, German Heart Centre Munich<br>*Epistatic effects in coronary disease risk* |
| 11:45 - 12:00 am | **Melanie Boerries**, University of Freiburg<br>*Delineating the Dynamic Transcriptome Response During Heart Regeneration in Zebrafish* |
| 12:00 - 12:15 pm | **Matthias Heinig**, Helmholtz Zentrum München<br>*Functional analysis of atrial fibrillation GWA loci* |
| 12:15 - 12:30 pm | **Sofia Hirth**, Ulm University Medical Center<br>*Paxillin-FAK-Vinculin signaling regulates cardiac contractility in zebrafish* |
| **12:30 - 02:30 pm** | **Lunch break**<br>**Poster Session** (12:30 - 01:30 pm odd numbers; 01:30 - 02:30 even numbers)<br>**Poster Walks** |
| **02:30 - 03:10 pm** | **e:Med Project Groups** |
| 02:30 - 02:40 pm | **Matthias Ganzinger**, Universität Heidelberg<br>*PG Informatics & Modelling* |
| 02:40 - 02:50 pm | **Marcella Rietschel**, ZI Mannheim;<br>**Ulrich Sax**, University Medical Center Göttingen<br>*PG Data Security & Ethics* |
| 02:50 - 03:00 pm | **Philip Rosenstiel,** University Hospital Schleswig-Holstein, Kiel<br>*PG Epigenetics & Sequencing* |
| 03:00 - 03:10 pm | **Holger Erfle, Manuel Gunkel**, BioQuant Center for Quantitative Analysis of Molecular and Cellular Biosystems, Heidelberg<br>*PG Processing of Imaging data* |

**03:10 - 03:30 pm** **Coffee Break**

**03:30 - 05:00 pm** **Session IV: Computational Approaches & Clinical Utilities - *Keynotes***
Chair: Ingo Röder

03:30 - 04:00 pm **Fabian Theis,** Helmholtz Zentrum München
*Integrating omics data in cohort studies*

04:00 - 04:30 pm **Thomas Höfer,** DKFZ Heidelberg
*Mathematical models and the emergence of chemotherapy resisters*

04:30 - 05:00 pm **Julien Gagneur,** LMU München
*Identification of novel causal genes in rare diseases: a Bayesian approach*

**05:00 - 05:30 pm** **Coffee Break**

**05:30 - 07:00 pm** **Session IV: Computational Approaches & Clinical Utilities – *Short Talks***
Chair: Hamid Noori

05:30 - 05:45 pm **Matthias Schlesner**, DKFZ Heidelberg
*Mutational and gene expression landscapes of tumor-xenograft pairs in PDAC reveal the strength of pure tumor models and differences in their cancerogeneity*

05:45 - 06:00 pm **Friedrich Feuerhake**, Hannover Medical School
*Parametrization and iterative improvement of agent-based mathematical models with spatial data from human biopsies*

06:00 - 06:15 pm **Cavin Ward-Caviness**, Helmholtz Zentrum München
*Novel approaches to understanding biological pathway perturbations associated with clinical phenotypes*

06:15 - 06:30 pm **Julia C. Engelmann**, University of Regensburg
*Improving causal effect estimation from virtual perturbations with accumulation IDA*

06:30 - 06:45 pm **Avidan U. Neumann**, Charité University Hospital, Berlin; University of Zurich
*Analysis of T-cell repertoire kinetics on single clone level shows immune correlate of Influenza vaccine protective response to newly emerged strains*

06:45 - 07:00 pm **Michal Or-Guil**, Humboldt University Berlin
*Systems medicine approach to personalized immunosuppressive treatment at early stage after kidney transplantation*

**07:00 - 10:00 pm** **Networking** (only with previous registration)
Bus shuttle from the venue to the historic center.

- From 8 pm **dinner in the Heidelberg historic center** at Kulturbrauerei (Leyergasse 6). Food is offered to you for free, drinks are asked to be paid by each participant.
- After dinner at 10 pm **Guided Tour** “Through the dark alleys of Heidelberg with the night watchman”.

## Wednesday, October 28, 2015

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| **08:30 - 09:00 am** | **Welcome Coffee** |
| **09:00 - 10:30 am** | **Session V: Cancer - *Keynotes***<br>Chair: Hartmut Goldschmidt |
| 09:00 - 09:30 am | **Angelika Eggert,** Charité University Hospital, Berlin<br>*Systems Medicine Approaches in Cancer Research* |
| 09:30 - 10:00 am | **Martin Peifer,** University of Cologne<br>*Comprehensive genomic profiles of small cell lung cancer* |
| 10:00 - 10:30 am | **Matthias Fischer,** University Hospital Cologne<br>*Telomerase activation by genomic rearrangements in high risk neuroblastoma* |
| **10:30 - 11:30 am** | **ELSA on Systems Medicine**<br>Chair: Matthias von Witsch |
| 10:30 - 10:35 am | **Matthias von Witsch**, DLR Projektträger Bonn<br>*Introducing ELSA on Systems Medicine* |
| 10:35 - 10:55 am | **Irene Schlünder, TMF e.V.**<br>*Challenges of Big Data for Data Protection in Biomedical Research* |
| 11:00 - 11:15 am | **Peter Dabrock**, University of Erlangen<br>**Rita Schmutzler**, University and University Clinics Cologne<br>*The ambivalent situation of BRCA mutation carriers. Transdisciplinary perspectives ELSA Project SYSKON* |
| 11:15 - 11:30 am | **Henrike Fleischer**, IMGB of the Universities Heidelberg and Mannheim<br>**Christoph Schickhardt**, University Hospital Heidelberg (NCT)<br>*Do patients have a right to obtain their genetic (raw) data from sequencing studies? ELSA Project DASYMED* |
| **11:30 - 12:00 am** | **Coffee Break** |
| **12:00 - 01:30 pm** | **Session V: Cancer – *Short Talks***<br>Chair: Angelika Eggert |
| 12:00 - 12:15 pm | **Katharina Deeg**, DKFZ Heidelberg<br>*Identifying telomere maintenance mechanisms in glioblastoma cell lines and primary tumor samples* |
| 12:15 - 12:30 pm | **Julia C. Engelmann**, University of Regensburg<br>*Causal modeling of stroma-cancer cell communication* |
| 12:30 - 12:45 pm | **Michael Bitzer**, University Hospital Tübingen<br>*Multiscale modelling of vascular dependent tumor growth in hepatocellular carcinoma (HCC) under therapy with transarterial chemoembolization (TACE)* |
| 12:45 - 01:00 pm | **Martin Siegemund**, University of Stuttgart<br>*Dimerized EGFR-targeted protein formats of single-chain TNF-related apoptosis inducing ligand (TRAIL) are highly effective antitumor therapeutics* |
| 01:00 - 01:15 pm | **Rienk Offringa**, DKFZ Heidelberg<br>*The TIPC project: T-cell therapy In Pancreatic Cancer* |
| 01:15 - 01:30 pm | **Alexander Schramm**, University Childrens`s Hospital Essen<br>*Mutational dynamics between primary and relapsing neuroblastoma* |
| **01:30 - 01:45 pm** | **Closing Remarks**<br>**Jeanette Erdmann**, Spokesperson of the e:Med Project Committee |
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| 26 | O-I-4 | Berenice Brandt | A multi-omics approach to decipher drug specific response signatures in the treatment of IBD | Christian-Albrechts-University and University Hospital Schleswig-Holstei |
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| 70 | O-V-4 | Katharina Deeg | Identifying telomere maintenance mechanisms in glioblastoma cell lines and primary tumor samples | DKFZ |
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# Oral Presentations
# I Epigenetics & Transcriptomics

## Dissecting epigenetic networks

Consortium CancerTelSys

**Presenting Author: Karsten Rippe**

Deutsches Krebsforschungszentrum (DKFZ) and Bioquant Center, Research Group Genome Organization & Function, Heidelberg, Germany

The cell nucleus lacks internal membrane boundaries. Free diffusive transport of proteins and RNA leads to rapid mixing of soluble components on the second time scale in a size dependent manner. Nevertheless, the cell can establish distinct heritable patterns of active and silenced chromatin in the absence of sequence alterations of the DNA genome. Hundreds of proteins are linked in large networks to 'write', 'erase' or 'read' about 140 different so-called epigenetic modifications of histone proteins and DNA. These chromatin signals in turn recruit chromatin remodeling factors or architectural chromatin components in a highly dynamic manner to regulate genome access for transcription, DNA repair, and replication machineries. Functional chromatin states control cellular programs that, for example, determine cell types during differentiation. Notably, these programs can be changed in response to environmental cues. The deregulation of epigenetic signaling is tightly linked to diseases as witnessed by the large number of recurrent mutations found in chromatin modifiers that are reported in recent cancer genome sequencing studies. The introduction to epigenetic networks presented will have a focus on histone modifications and will cover the following topics: (i) Epigenetic signals, their propagation and mechanisms for regulation of genome access. (ii) Information on cellular functions and their disease linked deregulation that can be obtained from mapping the epigenome. (iii) Approaches for the experimental and theoretical analysis of chromatin states involved in the regulation of gene expression.

# Epigenomics – from mapping to functional interpretation

**Presenting Author: Jörn Walter**

Saarland University, FR8.3 Genetik&Epigenetik, Germany,

Epigenetic concepts are greatly influencing our understanding of mechanisms controlling cellular development (epigenesis), the (in)stability of genetic regulation (functional genomics) and effects of (non-mendelian) inheritance. Epigenetic control involves multiple molecular levels including various forms of DNA-methylation, multiple histone modifications and numerous forms of non-coding RNAs. By combining these multiple layers the single genome of an organism is epigenetically “transformed” into hundreds of different cell type specific epigenomes during development and differentiation. We are just beginning to understand how this cell type specific epigenomic grammar is established. The „1000 epigenomes“ project launched by the International Human Epigenome Consortium IHEC aims to provide a comprehensive catalogue of cell type specific epigenomes of human cells in healthy and diseased state. In the first part of my talk I will summarize the data generated in IHEC with a focus on the DEEP (= german consortium) contribution . I will particularly discus the insights on genome wide epigenetic topologies that can be inferred from epigenome comparisons and their impact on functional and translational interpretation. In the second half I will discus experiments to understand the mechanisms controlling stable and unstable maintenance of epigenetic patterns in cells - and their potential impact on diseases.

http://ihec-epigenomes.org
http://www.deutsches-epigenom-programm.de

# Transcriptome profiling by RNA-sequencing and its clinical application exemplified in multiple myeloma

Consortium CLIOMMICS

**Presenting Author: Dirk Hose**

University Hospital Heidelberg

Clinical aims of RNA-sequencing (RNA-seq) in multiple myeloma are i) performing and reporting of sequencing based assessment of survival (prognosis), ii) therapeutic targets (e.g. CD38, B-cell maturation antigen (BCMA), Aurora-kinase, BRAF, ErbB-receptors), especially those present in a subfraction of patients, and iii) biological parameters (e.g. growth kinetics of malignant plasma cells) in clinical routine based on strategies used for gene expression profiling (GEP) by DNA-microarrays.

Transcriptome profiling by GEP allows prediction of survival, assessment of biological parameters, and therapeutic targets. Within the BMBF-funded CAMPSIMM-project, we have shown this to be possible in clinical routine within 4-6 weeks. We likewise showed that prognostic data can be integrated in a systems medicine approach and be reported using our gene expression report (GEP-report). Substituting GEP by RNA-sequencing holds two main advantages, first the investigated transcriptome is not limited to predefined sequences ("probesets") and thus additionally allows detection of mutated transcripts (e.g. BRAF-V600E mutation) and those erroneously or not sufficiently sensitively represented on DNA-microarrays (e.g. ErbB-receptors). This is of special importance as for two of these clinical grade inhibitors exist approved for other disease entities, i.e. Vemurafenib (BRAF) and Cetuximab (ErbB1). Further examples of (non-mutated) targets are CD38 (e.g daratumomab, isatuximab) and BCMA (antibody based treatment in development in a collaborative approach). Secondly, RNA-Seq needs lower amounts of material, important in diseases as multiple myeloma or e.g. for assessments from sorted cellular subfractions or fine needle biopsies, i.e. 1ng of RNA (vs. 100 ng for GEP). In the example of myeloma, this allows analysis and reporting of 90% of patients (vs. 80% for GEP). Main current challenges are the higher complexity and lower inter-group standardisation of RNA-sequencing approaches, e.g. regarding library preparation and bioinformatics analysis (e.g. normalisation, absence/presence of expression), and clinical reporting (RNA-Seq report vs. GEP-R) compared to GEP.

# A multi-omics approach to decipher drug specific response signatures in the treatment of IBD

Consortium SysINFLAME

**Presenting Author: Berenice Brandt**

Berenice Brandt2, Konrad Aden1,2, Ateequr Rehman1, , Johannes Bethge2, Susanna Nikolaus2, Dörthe Schuldt2, Mark Ellrichmann2, Raheleh Sheibani1, Philip Rosenstiel1 and Stefan Schreiber1,2

1 Institute of Clinical Molecular Biology, Christian-Albrechts-University and University Hospital Schleswig-Holstein, Campus Kiel, 24105 Kiel, Germany 2 First Medical Department, Christian-Albrechts-University and University Hospital Schleswig-Holstein, Campus Kiel, 24105 Kiel, Germany

Background: Current therapeutic interventions in inflammatory bowel disease aim to dampen the inflammatory response by blocking either specific signaling pathways (e.g. TNF-$\alpha$ or IL-6) or homing of leukocytes (anti-integrin antibodies). Although these therapeutic strategies are able to induce clinical response in IBD patients, the molecular mechanism underneath are not understood and objective criteria to confirm early reponse to therapy are missing. To analyse the mechanisms of anti-TNF-$\alpha$, anti-IL-6 and anti-integrin therapy we applied a deep characterization of selected IBD patients in response to therapy induction. Materials and Methods: IBD patients (Crohns Disease, Ulcerative Colitis) were subjected to either anti-TNF-$\alpha$ (Remicade®), anti-IL-6 (RoActemra®) or anti-integrin (Vedolizumab®) therapy. In addition to the clinical characterization, we performed ultrasound exams, minimal-model oral glucose tolerance tests and pulmonary function tests. To investigate the therapy response, biosampling (blood, sigmoid biopsies, stool) before and at 6 time points (+4h, +24h, +72h, +2weeks, +6weeks, +14weeks) after treatment initiation was performed. Mucosal biopsies will be employed for RRBS sequencing (methylation status), transcriptome analysis (RNAseq) and 16srRNA ribotyping. Results and Conclusion: By now we included 34 patients (20 female, 14 male) with active IBD, 17 suffering from ulcerative colitis, 16 from Crohn's disease, 1 from indetermined colitis. 15 patients received Infliximab, 17 patients Vedolizumab and 2 patients Tocilizumab. In this cohort 16 patients were categorized as responder, 5 as non-responder. First results of gene expression signatures and functional networks associated with early response will be presented. Multi-omics profiling along time series is able to identify changes in the treated gut mucosa as early as 4h after therapy induction. Further analyses will aim to decipher unique and common signatures of response and non-response between different therapies, which may ultimately help to stratify patients and guide personalized treatment decisions.

# The microRNAome as a Biomarker Signature for Brain Diseases

Consortium IntegraMent

**Presenting Author: Gaurav Jain**

Prof. Dr. Andre Fischer, Dr. Farahnaz Sananbenesi, Gaurav Jain

The German Center for Neurodegenerative Diseases (German: Deutsches Zentrum für Neurodegenerative Erkrankungen DZNE)

As described in WP1 our project we have started to profile epigenetic gene-expression in post-mortem brain tissue from schizophrenia (SCZ) and bipolar disease (BP) patients. A specific focus was the cell type specific analysis of DNA-methylation and DNA-hydroxymethylation (Munich) and the small-non coding RNAome (Göttingen), specifically the microRNAome. Especially the analysis of the microRNAome was suggested to be followed up in blood samples from SCZ patients to evaluate whether microRNA signatures are suitable biomarker. Albeit we did not yet publish research paper related to the project, we generated interesting data. As such, we are able to perform cell-type specific analysis of DNA-methylation but also found that the analysis of the nuclear RNAome can be informative about the cellular RNAome. We have by now analyzed two different brain regions, namely A9 and A24. In collaboration with the Cichon group (and Prof. Zilles; Jüllich) we also started to define epigenetic changes related to the brain architecture suggested by Zilles et.al. This data is at present still preliminary. We however have already interesting data on microRNAome changes in SCZ and BP patients. 57 mciroRNAs significantly differ when comparing A9 vs A24 from healthy individuals. In the A9 area we found that 24 microRNAs are significantly differentially expressed comparing BP to control individuals. Interestingly, in A24 we also detected 24 differentially expressed microRNAs, of which 5 were common. Performing the same analysis in the SCZ patients we detected 36 and differentially expressed microRNAs in A24 and A9, respectively, of which 7 were regulated in both brain regions. Of note 2 microRNAs were commonly regulated across brain regions in SCZ and BP patients. In addition specific signatures for each condition were detected. Selected microRNAs are now followed up via computational and mechanistic studies. We also have preliminary data analyzing the microRNAome in blood from SZC patients.


# Oral Presentations
# II Genome Editing

# Crispr/Cas9: The Revolution in Genome Editing

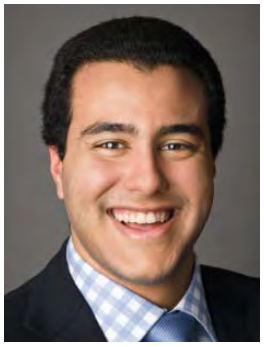
Consortia IntegraMent / SysMedAlcoholism, Demonstrator MitoPD

**Presenting Author: Wolfgang Wurst**

Institute of Developmental Genetics, Helmholtz Zentrum München, München, Germany

The discovery of the Crispr/Cas9 endonuclease from the bacterial adaptive immune system Crispr can be easily adapted and programmed to bind, cleave or modify eukaryotic DNA sequences using just a short guide RNA (sgRNA) as vehicle. Application of Cas9 is enabling the creation of sophisticated disease models by introducing precise point mutations, deletions, inversions and duplications. In addition, Crispr/Cas9 is broadening the genetically tractable organisms that can be used to study biological mechanisms during health and disease. This system can also be used to modulate gene transcription, and to change the epigenetic state of the genome in vitro and in vivo. Furthermore, Crispr/Cas9 technology has the potential for somatic gene correction in vivo. In this presentation, I will give an overview of the latest developments of Cripsr/Cas9 applications in disease modelling.

# Applications of CRISPR/Cas9 and Discovery of new CRISPR Systems



**Presenting Author: Omar Abudayyeh**

MIT, Harvard, Cambridge, USA

Microbial CRISPR-Cas systems are divided into Class 1, with multisubunit effector complexes, and Class 2, with single protein effectors. Currently, only two Class 2 effectors, Cas9 and Cpf1, have been described. Here, we describe a CRISPR-based method that uses catalytically active Cas9 and distinct single guide (sgRNA) constructs to knock out and activate different genes in the same cell. These sgRNAs, with 14- to 15-bp target sequences and MS2 binding loops, can activate gene expression using an active Cas9 nuclease, without inducing double-stranded breaks. We use these 'dead RNAs' to perform orthogonal gene knockout and transcriptional activation in human cells. Additionally, we go on to describe three more distinct Class 2 CRISPR-Cas systems. The effectors of two of the identified systems, C2c1 and C2c3, contain RuvC-like endonuclease domains distantly related to Cpf1. The third system, C2c2, contains an effector with two predicted HEPN RNase domains. We functionally characterize these new systems and show distinct new features compared to Cas9 and Cpf1 Class 2 effectors. Finally, comparative analysis indicates that Class 2 CRISPR-Cas systems evolved on multiple occasions through recombination of Class 1 adaptation modules with effector proteins acquired from distinct mobile elements.

# CRISVar: Generating structural variations to study the 3D organization of the genome in disease

**Presenting Author: Darío Jesús García Lupiáñez**

MPI for Molecular Genetics Berlin

Structural variations (SVs) represent a major source of variability in the human population and are often associated with disease. The study of these rearrangements using model systems has been classically hampered by labor, time and cost intensive targeting methods, often followed multiple breeding steps. The recent adaptation of CRISPR/Cas technology as a precise genome editing tool has opened new paths to study the human genome and its variations. Here we present the use of the CRISPR/Cas system to generate transgenic mice carrying large SVs in 10 weeks (CRISVar). CRISVar allows the induction of deletions, inversions and/or duplications in vivo with no apparent limitations regarding size or the targeted locus. In this talk, we will discuss how CRISVar can be broadly applied to model human pathogenic SVs and to study the role of 3D genomic architecture in gene expression and disease.

# Crispr/Cas9 technology for genome engineering in adult animals: disease modeling and therapeutic application

**Presenting Author: Hao Yin**

David H. Koch Institute for Integrative Cancer Research
Massachusetts Institute of Technology, Cambridge, USA

The clustered, regularly interspaced, palindromic repeats (CRISPR)-associated (Cas) system has been engineered into a powerful genome editing tool consisting of the Cas9 nuclease and a single guide RNA (sgRNA). The sgRNA targets Cas9 to genomic regions that are complementary to the 20-nucleotide (nt) target region of the sgRNA and that contain a 5'-NGG-3' protospacer-adjacent motif (PAM). Double-stranded DNA breaks generated by Cas9 at target loci are repaired by nonhomologous end-joining or homology-directed repair (HDR). CRISPR-Cas9 genome editing has been applied to correct disease-causing mutations in mouse zygotes and human cell lines, but delivery to adult mammalian organs to correct genetic disease genes has not been reported. To investigate the potential of CRISPR-Cas9–mediated in vivo genome editing in adult animals, we used a mouse model of hereditary tyrosinemia type I (HTI), a fatal genetic disease caused by mutation of fumarylacetoacetate hydrolase (FAH), the last enzyme in the tyrosine catabolic pathway. We demonstrate CRISPR-Cas9–mediated correction of a Fah mutation in hepatocytes in a mouse model of the human disease HTI. Delivery of components of the CRISPR-Cas9 system by hydrodynamic injection resulted in initial expression of the wild-type Fah protein in ~1/250 liver cells. Expansion of Fah-positive hepatocytes rescued the body weight loss phenotype. Our study indicates that CRISPR-Cas9–mediated genome editing is possible in adult animals and has potential for correction of human genetic diseases. Further, implementation of this promising technology requires safe and effective delivery of all of these components into the nuclei of the target tissue. We report the first therapeutically relevant formulations of CRISPR/Cas9 capable of inducing repair of a disease gene in adult animals with more than 10 folds higher efficiency, suggesting potential utility for a range of diseases.


# Oral Presentations
# Evening Lecture

# From Systems Biology to Systems Medicine
# -An Avalanche is coming-

**Presenting Author: Rudi Balling**

Luxembourg Centre for Systems Biomedicine (LCSB)

Biomedical research has changed and medicine will (have to) change. Are we prepared for what is ahead of us? Interdisciplinarity, integration and internationalization are just some of the challenges, all of them easier said than done. I will share some of my own personal attempts and reflections in trying to cope with the transition from systems biology to systems medicine.


# Oral Presentations
# III Cardiovascular Diseases

## Systems medicine in cardiovascular diseases

Consortium e:AtheroSysmed

**Presenting Author: Jeanette Erdmann**

University of Lübeck

Cardiovascular diseases are among the leading causes of death in Europe. Until now, prevention and therapy of its most disabling sequelae, i.e. coronary artery disease, heart failure, and stroke, aim at ameliorating traditional risk factors.
Recently, over 70 chromosomal loci as well as novel lifestyle factors have been identified affecting cardiovascular disease risk. Surprisingly, only a few of these disease markers mediate their effects via traditional risk factors. Thus, current treatment does not address all principle disease mechanisms. Future efforts should be directed at a multi-scale, patient-centered approach applying OMICs technologies including methylomics, transcriptomics, and metabolomics for quantifying the downstream impact of both genetic and life-style mediated risks.
E:Med consortia like: e:AtheroSysMed, DeCaRe, symAtrial, and SYMBOL-HF will use computational and mathematical modeling approaches to move beyond current state-of-the-art towards a holistic understanding of mechanisms and treatment options.
All these consortia bring together major national and international resources (e.g. prospective epidemiological and clinical samples with detailed OMICs data, as well as experimental data from animal models, like mice and zebrafish) and scientists from a wide spectrum of disciplines (e.g. clinicians, geneticists, epidemiologists, systems biologists, bioinformaticians, mathematicians).
The intention of these projects is i) to create innovative platforms for harmonizing complex data, ii) to identify intermediate phenotypes leading to disease, iii) to gain knowledge by functionally study animal models, and iv) to utilize these insights towards the implementation of personalized prevention and treatment strategies.

## Systems Medicine of Heart Failure – SMART

Demonstrator SMART

**Presenting Author: Sarah Nordmeyer**

Deutsches Herzzentrum Berlin

Patients with aortic valve stenosis (AS) suffer from clinical sequelae of pressure induced myocardial hypertrophy. Aortic valve replacement (AVR) is intended to prevent progression of maladaptive myocardial remodelling and to reduce the risk of irreversible heart failure (HF).

The onset and course of HF is triggered by a complex regulatory network that includes stressors (pressure overload by individual anatomical findings), intrinsic (genetic), environmental (regulating epigenetics) and modifying factors (such as hormones). The approach of the "Systems Medicine of Heart Failure – SMART" consortium is the integration of multiple patient specific information from molecular, cellular and organ level and ultimately of the whole human organism in order to develop individualized strategies for the prevention and management of HF. For this reason "SMART" interrelates models describing the interplay between genome, proteome and cell function, regulating hormones, tissue composition and hemodynamic whole organ function up to a whole body description of a patient and the patient cohort.

The ultimate goal is to demonstrate proof-of-concept tools for predicting disease evolution and efficacy of treatment in a given patient. To achieve this task SMART:

- Applies a modelling framework that couples multi-scale mechanistic models with in-depth genome/proteome, cell physiology and whole organ (biomechanical and fluid dynamic) models
- Subsequently, methods validity and relevance for "quantitative prediction" of treatment outcome is investigated in a clinical proof-of-concept trial of patients with AS (n=60 patients, 2 trial arms).
- More specifically, the pathophysiological response to surgical AVR and adjunctive pharmacological treatment with angiotensin receptor blockers (ARB) is investigated.

# Improved prediction of disease-associated SNPs in genome-wide association data by Bayesian modelling and data integration

Consortium e:AtheroSysMed

**Presenting Author: Johannes Soeding**

MPI für Biophysikalische Chemie, Göttingen

Getting the most out of valuable GWAS data requires more flexible models and overcoming the multiple testing problem

I will explain the advantages of designing Bayesian statistical models for the analysis of genome-wide association study (GWAS) data sets and for integrating heterogeneous information to improve predictions. Bayesian approaches allow us to formulate more detailed parametric models that better capture the presumed nature of the data and that will yield better results than classical hypothesis tests. Crucially, the parameters for these more detailed models can be learned from the data. Bayesian approaches also allow us to explore our data freely without multiple testing dilemma.

I will illustrate these points at the example of a Bayesian approach for predicting causal single nucleotide polymorphisms (SNPs) in GWAS data. The approach not only yields interpretable probabilities but should also improve the identification, fine mapping and ranking of SNPs. This is due to three technical advantages: (1) The approach considers all SNPs in a risk locus at once and therefore takes account of their strong local correlations due to genetic linkage. (2) It learns the distribution of effect sizes of SNPs and how it depends on local genomic features such as minor allele frequency, sequence conservation, DNase accessibility and chromatin modification profiles in various tissues, etc. (3) It can model gene-environment interactions. We parametrize the dependence of prior probability for causality and of the effect size distribution on these local genomic features and on the minor allele frequency using hyperparameters, and we learn these from the data by maximising the marginal likelihood. In the marginal likelihood the SNP effect sizes with their unavoidably large estimation errors are integrated out, which makes the estimate of hyperparameters very robust. Finally, I will point out a major flaw in the common practice to correct for confounding variables and suggest a simple solution.

# Analysis of coxibs pleiotropic molecular targets reveals novel genomic loci conferring coronary artery disease risk

Consortium e:AtheroSysmed

**Presenting Author: Ingrid Braenne**

Ingrid Brænne1,2, Christina Willenborg1,2, Benedikt Reiz1,2, CARDIoGRAM Consortium, CARDIoGRAMplusC4D Consortium, Jeanette Erdmann1,2, Heribert Schunkert3,4

1Institut für Integrative und Experimentelle Genomik, Universität zu Lübeck, 23562 Lübeck, Germany; 2DZHK (German Research Centre for Cardiovascular Research), partner site Hamburg/Lübeck/Kiel, 23562 Lübeck, Germany; 3Deutsches Herzzentrum München, Technische Universität München, 80636 München, Germany ; 4DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, 80636 Munich, Germany

Background: Genomic variants affecting disease risk may advise drug discoveries and predict potential drug side effects. Here we reversed this approach and studied molecular targets of a drug class with known side effects relating to coronary risk, cyclo-oxygenase-2 inhibitors (coxibs), to detect signals for coronary artery disease (CAD) in a genome-wide association study (GWAS). Methods and Results: A Drug Gene Interaction Database search identified 47 gene products to be affected by administration of a coxib. We traced association signals in 200-kb regions surrounding these genes in the CARDIoGRAMplusC4D 1000G GWAS meta-analysis on 60,801 CAD cases and 123,504 controls. We identified 5 loci with significant association after Bonferroni correction for the number of genes tested, i.e. $P < 2\times10\text{-}4$. To evaluate how many genes show association by chance, we re-ran the pipeline for drugs not reported to cause coronary side effects. Studying genes affected by epilepsy, ataxia and acne drugs (n=56), we did not find any comparable association in the CAD GWAS meta-analysis (P=0.02 versus number of signals in coxib-related genes). We then went on to seek for replication of the association signals in the four coxib-related genes. Studying further 24,012 CAD cases and 79,039 controls, all five lead SNPs showed the same direction of effect, displaying robust association signals in a meta-analysis in MMP9 (rs7270354, $P=6.76\times10\text{-}8$), BCAR1 (rs4888383, $P =7.99\times10\text{-}8$), VEGFA1 (rs6905288, $P=7.45\times10\text{-}7$), CACNA1E (rs556321, $8.27\times10\text{-}6$) and CYP3A4 (rs2572000, $P=6.29\times10\text{-}5$). . Conclusion: Pleiotropic or off-target effects may affect the safety spectrum of drugs and thus need consideration in genomic investigations aimed at predicting the benefit-risk ratio of pharmacological treatment. Here a focused search directed at such targets of a drug known to increase coronary risk identified 5 novel genomic loci displaying association with CAD risk.

# Data warehouse for coronary artery disease

Consortium e:AtheroSysMed

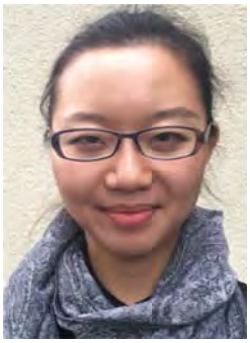
**Presenting Author: Helmut Spengler/Thorsten Kessler**

Helmut Spengler [1,*], Thorsten Kessler [2,*], Rainer Blaser [1], Lingyao Zeng [2], Winfried März [3], Adnan Kastrati [2,4], Heribert Schunkert [2,4], Klaus A. Kuhn [1,4]

[1] Institut für Medizinische Statistik und Epidemiologie, Technische Universität München, Munich, Germany [2] Deutsches Herzzentrum München, Klinik für Herz- und Kreislauferkrankungen, Technische Universität München, Munich, Germany [3] Synlab Akademie, Synlab Labordienstleistungen, Mannheim, Germany [4] Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK) e.V., partner site Munich Heart Alliance, Munich, Germany [*] contributed equally

Introduction: Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in western countries. Recent research activities have led to an accumulation of large amounts of clinical and OMICs data, that enable systems medicine approaches to gather deeper understanding of the disease. Aim: The aim of this project was to use business intelligence methods for an improved overview of different attributes collected in the context of coronary artery disease. The capability for inclusion of different datasets and continuous expansion is an important factor. Methods and Results: We utilized the QlikView Business Discovery platform for the generation of the data warehouse. As a starting point, patients that underwent coronary angiography at the German Heart Centre Munich were included. We assessed the following phenotypes (gender, availability of DNA/blood, age at last coronary angiography, max. stenosis grade, bypass graft lesion, percutaneous coronary intervention (PCI), ST-segment elevation myocardial infarction (MI), acute coronary syndrome, atrial fibrillation, alive/dead, previous bypass surgery, previous PCI, previous MI). Additionally, we included genotypes and genetic metadata of the known CAD risk loci. In summary, the data warehouse consists of more than 72,000 patients. Genotype data is available for 2,400 of these patients. Age distribution, presented as decades, maximal stenosis grade and genotype distribution are graphically displayed. All phenotypes and genotypes are displayed in real-time. Analyses can be performed phenotype- and genotype-centred. Conclusion and Outlook: The data warehouse supports real-time data mining and hypothesis generation in patients suffering from CAD. Currently, the capacities for including more genotypes and phenotypes are expanded. Additionally, harmonization strategies to include further datasets, e.g. phenotype-genotype but also OMICs data, are evaluated to provide a comprehensive evaluation tool for CAD.

# Epistatic effects in coronary disease risk



Consortium e:AtheroSysMed

**Presenting Author: Lingyao Zeng**

Lingyao Zeng, Nazanin karbalai, Bertram Müller-Myhsok, Heribert Schunkert

Deutsches Herzzentrum München, Technische Universität München and Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK), partner site Munich Heart Alliance (L.Z., H.S.) Department of Statistical Genetics, Max-Planck-Institute of Psychiatry, München, Germany (N.K., B.M.M.)

Modern large-scale genome-wide association studies have identified more than 50 genetic loci affecting coronary artery disease (CAD) risk. However, these risk loci additively explain only a fraction of CAD heritability. Gene-gene interactions or epistatic effects have been proposed to be existing ubiquitously in biology, and to be helpful in better understanding of genetic mechanisms.

In this study, we aimed at investigating the potential epistatic effects among the known CAD risk loci with a data-driven strategy. We harmonized individual level data across 9 genome-wide association studies (GWAS) of European ancestry. Altogether we assembled > 13,000 CAD cases and > 13,000 controls in order to alleviate the heavy burden of multiple testing and boost the power. Utilizing a GPU-based software we exhaustively performed regression for all possible pairwise interaction combinations between variants at or in vicinity of known genetic risk loci of CAD. For each variant all possible genotype models (dosage, dominant, heterozygous, recessive) were coded and tested.

Here we show, several significant epistatic effects are found with concordance of direction in 9 cohorts between variants at known CAD risk loci, either across different chromosomes or on the same chromosome. Furthermore, in a cohort of >700 individuals with >12,000 gene expression levels measured in monocytes and macrophages, several pairwise interacting epistatic loci show correlations with some interesting genes involved in coronary disease-related pathways.

This study presents the first evidence, to our knowledge, for epistatic effects in coronary disease risk, and provides further explanations of the disease heritability.

# Delineating the Dynamic Transcriptome Response During Heart Regeneration in Zebrafish

Junior Research Alliances DeCaRe

**Presenting Author: Melanie Boerries**

Hagen Klett a,b Gergana Dobreva a,c David Hassel a,d Florian Leuschner a,d, Hauke Busch a,b and Melanie Boerries a,b

a DeCaRe Junior-Consortium b Systems Biology of the Cellular Microenvironment Group, IMMZ, ALU, Freiburg; German Cancer Consortium (DKTK),Freiburg; German Cancer Research Center, Heidelberg c Goethe University, Frankfurt am Main; MPI for Heart and Lung Research, Bad Nauheim d University Hospital Heidelberg, Internal Medicine III, Department of Cardiology, Angiology and Pneumology

The human heart has a very limited capability to regenerate after injury. Therefore, loss of cardiomyocytes, e.g. due to myocardial infarction, often results in heart failure and death. Until now it is not clear why the human heart is unable to regenerate after a myocardial infarction. In contrast to humans, zebrafish are able to fully regenerate their hearts, leaving no trace of injury behind. Therefore this animal poses a suitable model to elucidate the capability for cardiac regeneration and by similarity leading to improved therapeutic interventions in humans. To obtain a holistic overview on the transcriptional processes and time sequential pathway activity during cardiac regeneration in zebrafish we analyzed the transcriptomes of whole hearts at days 1, 4, 7, 14, 21, 30 and 45 post cryoinjury. Functional analysis revealed both transient and persistent processes over time, involving inflammation and development as well as cell cycle, respectively. In detail, regeneration started with the up-regulation of cell cycle, development and apoptosis related genes, followed by DNA repair and inflammation on days 4 to 7. Cardiac tissue specific development processes as well as endothelial cell migration were transiently up-regulated around day 14, while cell division, inflammation and endothelial cell migration processes persisted through days 21 and 30 post injury. These processes are well in line with longitudinal echocardiography after cryoinjury, starting with a decreased fractional shortening and ejection fraction on day 1 and returning to normal sham levels until days 14-30. This data revealed how heart regeneration follows a well-orchestrated pattern of time-sequential pathway activation that will be studied in molecular detail within the DeCaRe consortium. As part of the DeCaRe initiative, miRNA and methylome data will be included.

# Functional analysis of atrial fibrillation GWA loci

Junior Research Alliance symAtrial

**Presenting Author: Matthias Heinig**

Matthias Heinig (1), Julia Krause (2,3), Arne Schillert (4), Renate Schnabel (2,3), Sebastian Schäfer (5), Stuart Cook (5), Norbert Hübner (6) and Tanja Zeller (2,3)

1. Institute of Computational Biology, Deutsches Forschungszentrum für Gesundheit und Umwelt, Helmholtz Zentrum München, 85764 Neuherberg, Germany

2. Clinic for General and Interventional Cardiology, University Heart Center Hamburg, Hamburg, 20246, Germany

3. German Center for Cardiovascular Research (DZHK e.V.), partner site Hamburg, Lübeck, Kiel, 20246, Germany

4. Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, Universitätsklinikum Schleswig-Holstein, Lübeck, Germany

5. Cardiovascular & Metabolic Disorders Program, Duke-NUS Graduate Medical School, Singapore

6. Genetics and Genomics of Cardiovascular Diseases, Max Delbrück Center for Molecular Medicine, Berlin, 13125, Germany

Background: Atrial fibrillation (AF) is the most common arrhythmia in the general population. AF has a heritable component, which has led to the identification of 12 AF risk loci through genome wide association (GWA) studies so far. However, the molecular mechanisms underlying these loci remain largely unknown. Methods and Results: We analysed SNPs of the 12 previously identified AF loci to identify functional candidate genes. For the 30 lead SNPs we obtained proxy SNPs with linkage disequilibrium Rsq > 0.8, determined from the 1000 genomes reference population. Proxy SNPs were annotated with epigenetic information from the Epigenomics roadmap project, binding sites of microRNA and RNA binding proteins, as well as expression quantitative trait loci (eQTL) in the left ventricle of the heart. As strongest functional candidates we identified six cis-eQTL genes in four distinct loci (P < 1e-5): MYOZ1, FUT11, SYNE2, PRRX1 and a long noncoding RNA (lncRNA) in the PRRX1 locus. MYOZ1 was previously identified as cis-eQTL in atrial tissue, while SYNE2 and PRRX1 and the lncRNA constitute novel findings. Conclusion: By integrative data analysis, we have identified one known and three novel functional AF candidate genes. We are currently characterizing differential expression of these candidate genes in cohort of AF subjects. To analyse the AF-related pathways in vitro experiments in cell culture, such as siRNA-mediated silencing or overexpression of candidate genes will be performed.

# Paxillin-FAK-Vinculin signaling regulates cardiac contractility in zebrafish

Junior Research Alliance SYMBOL-HF

**Presenting Author: Sofia Hirth**

University Hospital of Ulm Internal Medicine II Molecular Cardiology Albert-Einstein Allee 23 89081 Ulm

Paxillin is a focal adhesion-associated protein that serves as an adapter for other signaling molecules such as Focal Adhesion Kinase (FAK) or Vinculin. Moreover, Paxillin interacts with the Integrin-linked Kinase (ILK)-Parvin-Pinch (IPP) complex via binding to β-Parvin and ILK. Recently, we have shown that the IPP complex is an essential part of the cardiac mechanical stretch sensor controlling contractility by granting Protein Kinase B (PKB/AKT) signaling in cardiomyocytes. In this study, we show that targeted gene inactivation of Paxillin in zebrafish embryos, results in progressive decrease of cardiac contractility and heart failure. Since this phenotype resembles that observed in ILK-, PINCH-, or Parvin deficient zebrafish embryos, we next evaluated whether this is due to destabilization of the IPP-complex as observed by ablation of ILK, PINCH or Parvin. Paxillin deficiency does not interfere with IPP complex stability and PKB activation, suggesting an IPP-PKB-independent pathomechanism in Paxillin-deficient embryos. However, we find that Paxillin deficiency leads to the destabilization of its binding partners FAK and Vinculin. Remarkably, inactivation of either FAK or Vinculin, leads to contractile dysfunction and heart failure as observed for Paxillin-deficient embryos, again without affecting IPP-complex stability or PKB signaling. These findings highlight an essential role of Paxillin in controlling cardiac contractility via its interaction with FAK and Vinculin, independent of IPP-PKB-mediated signaling in zebrafish cardiomyocytes.


# Oral Presentations
# IV Computational Approaches & Clinical Utilities

## Integrating omics data in cohort studies

Consortium SYS-Stomach

**Presenting Author: Fabian Theis**

Helmholtz Zentrum München
http://comp.bio

Systems medicine may be defined as the implementation of systems biology approaches in medical research and practice. Many disease modeling approaches are based on case-control or population cohort data. In this talk, such cohort data paired with cellular quantification of transcriptomics or other omics data sets are considered. The most common biomedical questions are associations of particular observations with an outcome or a SNP, which result in mostly univariate regression problems. Here, I will review and discuss a few recent approaches towards a multivariate integration of such data, from simple correlation analysis to graphical modeling. Applications to the analysis of metabolomics data will be shown.

# Mathematical models and the emergence of chemotherapy resisters

Demonstrator SYS-GLIO

**Presenting Author: Thomas Höfer**

Division of Theoretical Systems Biology, German Cancer Research Center (DKFZ), Heidelberg, Germany

Overexpression of MYC proteins predisposes to therapy resistance in many cancers. We have studied the mechanisms through which the amplification of the MYCN oncogene in neuroblastoma drives tumor growth and shapes the response to chemotherapy. In this talk I will discuss how we used data-driven mathematical modeling to integrate genomic, biochemical and live-cell imaging data on neuroblastoma proliferation and apoptosis. The model predicts, and experimental tests validate, that both cell proliferation and cell-cycle arrest upon chemotherapy are governed by a bistable molecular switch. Several target genes of MYCN synergize to perturb this switch. These quantitative mechanistic insights guided us in elucidating the properties of a subpopulation of MYCN-amplified cells that survive chemotherapy, evade cellular senescence thereafter, and thus support clonal regrowth. We provide initial evidence that the molecular makeup of these ‘resister cells’ can be exploited for developing new approaches to first-line treatment, choosing appropriate combinations of chemotherapy and targeted drugs.

# Identification of novel causal genes in rare diseases: a Bayesian approach

Junior Researach Alliance mitOmics

**Presenting Author: Julien Gagneur**

LMU München

Identifying genetic causes of rare disorders from genome sequencing data is a statistically challenging task because the causal variants are extremely rare if not unique to individual patients. Hence, classical statistical testing, even applied to predefined groups of variants, has poor sensitivity. Consequently, causal gene identification for rare diseases is usually done by a combination of stringent variant frequency filters, followed by manual inspection. Here, we propose a Bayesian approach to candidate gene prioritization that integrates prior information of penetrance, known causal genes, molecular pathways and protein-protein interaction networks. Additionally, a supervised machine learning approach is applied to optimally combine the predictions of the developed models. The models were applied to a whole-exome sequencing dataset of about 400 mostly unrelated cases diagnosed with a mitochondrial disease and 125 controls. Sensitivity for recovering 75 known causal genes in a cross-validated fashion was used to benchmark the models. The Bayesian approaches showed increased sensitivity over statistical testing. Highest sensitivity -40% in the 100 most highly ranked predictions- was reached using the machine learning approach. Our method is general and could be applied to other rare diseases with a few known causal genes.

# Mutational and gene expression landscapes of tumor-xenograft pairs in PDAC reveal the strength of pure tumor models and differences in their cancerogeneity

Consortium PANC-STRAT

**Presenting Author: Matthias Schlesner**

Octavio Espinosa1, Tobias Bauer1, Zuguang Gu1, Jing Yang1, Matthias Schlesner1, Roland Eils1234

1 Division of Theoretical Bioinformatics, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, Heidelberg, 69120, Germany. 2 Heidelberg Center for Personalized Oncology, DKFZ-HIPO, DKFZ, Im Neuenheimer Feld 267, Heidelberg, 69120, Germany. 3 Institute of Pharmacy and Molecular Biotechnology, and Bioquant Center, University of Heidelberg, Im Neuenheimer Feld 267, Heidelberg, 69120, Germany. 4 Translational Lung Research Center Heidelberg (TLRC), German Center for Lung Research (DZL), University of Heidelberg, Germany.

Pancreatic ductal adenocarcinoma (PDAC) are often treated as single disease, despite notable genetic heterogeneity. Genetic analysis is hampered due to the difficulty of obtaining biopsies with high tumor purity. Characterizing individual variability to understand the underlying biology and to develop precision strategies is one of the forefront issues to improve PDAC treatment. Our cohort consists of 114 primary tumor samples with whole exome data and 26 xenografts derived from these same patients. Initial investigation indicated low tumor purity in most samples and discordance of purity estimates from molecular markers and pathology. To address this, we developed a sensitive variant pipeline to call single nucleotide polymorphisms (SNVs). Characterizing the genomic landscape of small mutations (SNVs and Indels) we found significantly higher tumor purity in xenograft samples allowing better recall of critical genes involved in PDAC carcinogenicity. We are able to trace mutations of subclones giving rise to the xenografts and subsequent evolution of xenograft-specific subclones. Clustering analysis and comparative characterization of the mutational profiles recalls previously identified genes and several novel genes that show key differences in tumor development between primary tumor and xenografts. RNAseq analysis of 54 primary tumors and 19 xenografts reveals strong variant levels of cell-type composition. Most protruding, PTPRC, a marker of inflammatory infiltrates, is highly expressed in all tumors. Moreover, INS (islet cells) and PNLIPR2 (normal pancreas parenchyma) exhibit high presence in > 50% of samples, and LEP (fat) can be detected in a smaller number of samples. Nevertheless, the PDAC -marker KR19 is also strongly expressed in all samples. Thus, tumor expression profiles are likely to be strongly influenced by non-tumor cell-specific expression hampering the ability to properly identify subtypes or subtype-specific genes. The xenograft expression profiles form a distinct cluster separate from the tumors. Similarities of corresponding pairs of tumor-xenograft are limited to invariant gene-families expressed at low levels. Strikingly, in all of the xenograft samples, non-tumor specific marker gene levels are at minimum while KRT19 levels are high. Taken together, these results support the evidence from exome sequencing that xenografts are potentially better models of PDAC.

# Parametrization and iterative improvement of agent-based mathematical models with spatial data from human biopsies

Consortium SYSIMIT

**Presenting Author: Friedrich Feuerhake**

F. Feuerhake (1), G. Apou (2), R. Schönmeyer (3), N. S. Schaadt (1), J. C. A. Lopez (4), A. Uvarovskii (5), N. Krönke (1), G. Forestier (6), C. Wemmert (2), H. Hatzikirou (4), M. Meyer-Hermann (5)

(1) Institute of Pathology, Hannover Medical School, Germany. (2) ICube (Image Analysis & Computational Science Laboratory), Université de Strasbourg, France. (3) Definiens AG, Munich, Germany. (4) Center for Advancing Electronics (cfAED), Technische Universität Dresden, Germany. (5) Department of Systems Immunology and Braunschweig Integrated Centre of Systems Biology, HZI, Germany (6) MIPS (Modélisation, Intelligence, Processus et Systèmes), Université de Haute-Alsace, Mulhouse, France

Background: The current lack of innovative approaches to evaluate biopsies for immune cells is a major bottleneck for the success of personalized immunomodulatory therapy. SYSIMIT uses an interdisciplinary systems medicine approach to overcome this gap by integrating advanced image analysis technologies with dynamic mathematical models. We propose new ways to interpret the “snapshot” of a clinical biopsy in the context of improved understanding of underlying dynamic processes of cancer and transplantation immunology. Computational approach: As platform for knowledge-driven image analysis Definiens Software is used in combination with tailored approaches to disease-specific detection of relevant regions of interest (ROIs), which includes development of disease-specific terminologies for implementation of expert knowledge in analysis workflows. A newly available module for generic nuclei detection in a variety of IHC stains provides a complementary basis for quantitative read-outs, like e.g. spatial distribution of cell type densities. For collaborative developments, result transfer between project partners has been established using Definiens Result Containers, which use the hdf5 data model and thus allow for a flexible exchange of image analysis results between processing steps at different resolutions. To translate underlying biological processes into data comparable with biopsy images, mathematical models were implemented as 2/3D agent-based frameworks for simulation of molecule distribution, cell migration and interaction. Results and perspectives towards clinical utilities: As conventional terminology based on disease-driven (ICD, SNOWMED) or anatomy-driven systems showed significant limitations for computation of relevant ROIs in breast and renal tissue, custom terminology was developed to define high-quality datasets for the training and evaluation of machine learning-based image analysis tools. The resulting tools efficiently automate the detection of biologically relevant ROIs in high-resolution whole slide images for various staining procedures. Integrating the read out of disease-specific, modular image analysis with agent-based modeling platforms, we established frameworks to investigate the dynamics of inflammation in kidney and breast biopsies. This brings the project closer towards the disease-overarching goal of identifying novel predictive immune cell patterns to determine risk for humoral graft rejection and oncogenic events in hereditary breast cancer.

# Novel approaches to understanding biological pathway perturbations associated with clinical phenotypes

Consortium e:AtheroSysMed

**Presenting Author: Cavin Ward-Caviness**

Cavin Ward-Caviness1, Kieu Trinh Do2, Jan Krumsiek2, Christian Gieger3, Fabian Theis2, Annette Peters1

1. Helmholtz Center Munich, Institute of Epidemiology II
2. Helmholtz Center Munich, Institute of Computational Biology
3. Helmholtz Center Munich, Department of Molecular Epidemiology

Complex diseases may arise from multiple perturbations in biological pathways. Current approaches often dissect pathways into individual associations which can miss synergistic or compounded effects. We present two methods that use all perturbations in a pathway to discover those that differ according to the state of a given clinical phenotype, i.e. cardiovascular disease cases versus controls.

Our first approach, Differential Activity of Pathways Assessment (DAPA), summarizes the correlations amongst all members of a pathway, in order to determine which pathways have differential overall correlations amongst their constituents. A stronger overall correlation between pathway constituents is often interpreted as more active regulation of the pathway. Our second approach, Topological Assessment of Pathway Differences (TAPD), examines topological differences in a pathway by comparing the edges that are present in one clinical state but not the other. Clinical state specific pathway edges can reflect underlying biology, e.g. gene deletions. DAPA samples from a given distribution to determine the p-value, while TAPD uses permutations to assess the significance of the pathway differences.

As a proof of concept we investigated sex specific differences in pathways extracted from a metabolite correlation network using the KORA F4 cohort (N = 1756; 903 females, 853 males). Pathways were based on annotations provided by Metabolon®, the creator of the metabolite assessment platform. Tryptophan metabolism was the most significant pathway in both methods. DAPA indicated that the tryptophan metabolism pathway is more active in females ($P = 1.3x10-3$), while TAPD revealed that 12 pathway edges differed between the sexes ($P = 0.0022$, 5000 permutations). Tryptophan is a member of the serotonin production pathway, whose regulation is known to differ by sex.

Thus, we have developed two methods that account for all perturbations in a pathway to assess differences in topology or activity.

# Improving causal effect estimation from virtual perturbations with accumulation IDA

Demonstrator MMML-Demonstrators

**Presenting Author: Julia C. Engelmann**

Franziska Taruttis, Rainer Spang, Julia C. Engelmann

Statistical Bioinformatics, University of Regensburg, Germany

To study biological networks, perturbation of individual players and observing resulting effects is a commonly used, but time- and resource-intensive approach. Recently, a statistical algorithm called 'Intervention calculus when the Directed acyclic graph is Absent' (IDA), has been proposed to derive causal effects solely from observational, that is, unperturbed gene expression data. The observational data is used to derive a partial causal network based on conditional independence tests. This network can then be statistically 'queried' to find all genes which would change their expression upon perturbation of gene X. Querying all genes X one-by-one allows to identify genes in the network with large causal effects on other genes. The major limiting factor in causal discovery is the poor accuracy of estimated networks, especially for low sample sizes typical in biological and medical applications. Since it is difficult to improve on the quality of estimated networks, we propose to use the information from imperfectly estimated networks more efficiently. This is done with a novel re-sampling strategy which collects, for each gene pair, causal effects derived from many sub-sampled networks, where each network is estimated from only a subset of the samples (e.g. 50%). The many networks are used to estimate causal effects, then, for each gene pair, the frequencies of causal effects estimated from the different networks are smoothed, and the most frequent effect size for this gene pair is identified. This procedure is based on the assumption that even if the relevant network properties are estimated in only a fraction of the sub-samples, they will still accumulate around the true effect size, whereas effect sizes from wrong networks will scatter within a large range of values. Because of the accumulation of causal effect sizes, we termed our approach 'accumulation IDA' (aIDA). We could show that aIDA improves the performance of causal discoveries on both simulated and real yeast datasets with respect to the number of true positives versus the number of false positives especially among the top predictions with largest effect sizes. The higher reliability of top causal effect predictions results in more promising candidates for future functional studies.

# Analysis of T-cell repertoire kinetics on single clone level shows immune correlate of Influenza vaccine protective response to newly emerged strain

Consortium e:Kid

**Presenting Author: Avidan U. Neumann**

Avidan U. Neumann (1,2), Mikalai Nienen (1,3), Leon Kuchenbecker (1), Ulrik Stervbo (1,3), Jochen Hecht (1) , Andreas Thiel (1) and Nina Babel (1,3)

1) BCRT, Charite University Hospital, Berlin, Germany. 2) Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland. 3) Marien Hospital Herne, Ruhr University, Bochum, Germany.

Introduction: Better understanding of the correlates of protective vaccination against newly emerged Influenza strains is of high importance for public health. Here we used next generation sequencing (NGS) of the T-cell receptor (TCR) repertoire to characterize the kinetics of single T-cell clonotypes upon vaccination. Methods: Seasonal tri-valent Influenza vaccine, including the newly emerged H1N1 California (CA) strain, was administrated to 21 healthy volunteers (reported here results for first 6 with completed analysis). TCR-repertoire of memory, naïve and regulatory CD4 T-cells, specific for the 3 vaccine antigens, was analyzed at 5 time points within 28 days post vaccination by deep sequencing. The kinetics of each single clonotype (mean 5,338 clonotypes per sample) was determined and clustering was used to obtain the least number of kinetic patterns that best covers all the single clonotypes kinetics. Results: 5-20% of the dominant CD4-memory clonotypes were detected at 3-5 time points; thus allowing to determine hundreds of single clonotype kinetics in each vaccinee. A small number (3-5) of significantly different kinetic patterns (e.g., high at baseline then decline, expansion with single peak at day 7-14, the same with second peak at day 28) was enough to describe 70-90% of the clonotypes kinetics. Strikingly, in the 3 patients that stayed non-protected to the CA strain, 40-80% of the dominant CD4-memory clonotypes with kinetics were detected at baseline, as compared to none in the 3 patients that became protected. Conclusion: TCR-repertoire analysis allows determining the kinetics of immune response to vaccine on a clonal level, which is not possible by using classical approaches such as FACS or Tetramer analysis. Furthermore, our preliminary results indicate that clustering of these single clone kinetic patterns may have an important clinical utility in predicting and better understanding the protective vaccine response to newly emerged Influenza strains.

# Systems medicine approach to personalized immunosuppressive treatment at early stage after kidney transplantation

Consortium e:Kid

**Presenting Author: Michal Or-Guil**

Dr. Michal Or-Guil (1) Dr. Chris Bauer (2) Dr. Johannes Schuchhardt (2) Prof. Dr. med. Nina Babel (3)

(1) Department of Biology, Humboldt University Berlin (2) MicroDiscovery GmbH, Berlin (3) Medical Clinic/Nephrology, Charité, Berlin; Marien Hospital Herne, UK Ruhr-Univ. Bochum

The kidney is one of the most transplanted organs wordwide, with tens of thousands transplantations occurring every year. While currently transplant patients receive standard immunosuppressive therapy disregarding individual risk profile (“one size fits all”), previous studies showed that such unbalanced therapy might be “too weak” for rejection-high-risk group or “too strong” for rejection-low-risk group. Subsequently, the former group develops graft rejection, whereas the latter group is unnecessarily exposed to high drug burden causing severe side effects. Prediction of complication and subsequent adjustment of immunosuppressive therapy is not possible now, since the clinical course is regulated by various parts of the immune system (T-cells, B-cells; cytokines, chemokines) at different time scales. This complexity, together with the lack of early complication markers, hinders targeted early therapeutic decisions. In order to overcome this problem, for the first time, complex clinical patient data from a large patient cohort following one year after transplantation is analysed in combination with different experimental data. Central to our approach is a low-dimensional, heuristic, time-resolved model that describes the risk for acute graft rejection and viral reactivation as a function of clinical status and immunosuppressive medication of individual patients. This model will be improved and tested during the course of the project using prognostic makers extracted from clinical and experimental data through both explorative- and hypothesis-driven analyses. These includes, for instance, the comparison of statistical antibody landscapes or deep-sequencing derived T-cell repertoires, as well as the establishment of clinically relevant mechanisms of immune protection from cytokine profiles. The overall aim is to establish a tool for support of personalized treatment of kidney transplant recipients which shall be validated in a follow-up prognostic study.


# Oral Presentations
# V Cancer

# Systems Medicine Approaches in Cancer Research

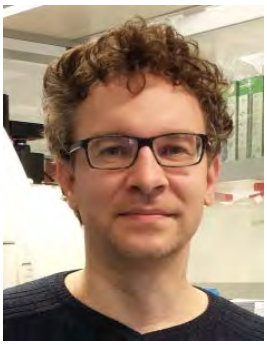
Consortium SYSMED-NB

**Presenting Author: Angelika Eggert**

Charité Universitätsmedizin Berlin, Klinik für Pädiatrie mit Schwerpunkt Onkologie und Hämatologie

A major challenge impeding favorable treatment outcomes in cancer patients arises from the complex nature of the disease, in particular from the cellular, intratumoral and intertumoral heterogeneity and the countless number of dysfunctional molecular networks resulting from genetic and environmental perturbations. Systems biology, with its holistic approach to understanding fundamental principles in biology, and the empowering technologies in genomics, epigenomics, proteomics, metabolomics, single-cell analysis, liquid biopsies and computational strategies, enable a comprehensive approach to cancer medicine, which strives to unveil the pathogenic mechanisms of tumor entities and subgroups, identify disease biomarkers and develop new strategies for drug target discovery. The integration of multidimensional high-throughput 'omics' measurements from tumor tissues and corresponding blood specimens, together with new systems strategies for diagnostics, allows the identification of cancer biomarkers which will enable early diagnosis, risk stratification, assessment of disease progression, evaluation of patient response to therapy and early identification of relapses. This session will provide an introduction to and overview of the field.

# Comprehensive genomic profiles of small cell lung cancer



Consortium SMOOSE

**Presenting Author: Martin Peifer**

University of Cologne

The identification of biologically relevant cancer genome alterations from large-scale sequencing efforts requires a systematic computational data analysis. Here, we present our approach to integrate various genomic datasets to identify such alterations in small cell lung cancer (SCLC).
Small cell lung cancer occurs in about 16% of all lung cancer patients and is particularly aggressive. To decipher the genomic landscape of these tumors we sequenced the genomes of 110 and the transcriptomes of 81 patient specimens. In nearly all sequenced tumors, we found a bi-allelic mutational deactivation of the tumor suppressor genes TP53 and RB1. Two cases – where RB1 was completely intact – harbored chromothripsis events that affected chromosome 3 and 11 and resulted in an overexpression of cyclin D1 as an alternative mechanism of RB1 suppression. Thus, the loss of the two tumor suppressors TP53 and RB1 is a curial event in the pathogenesis of SCLC. In addition, we found recurrent genomic rearrangements that created an oncogenic version of TP73. Furthermore, we observed a high mutation frequency of damaging mutations affecting NOTCH family genes, suggesting a tumor suppressive role of NOTCH. This notion was confirmed in a pre-clinical SCLC mouse model that showed a reduced number of tumors and extended survival after Notch activation.
In summary, our proposed systematic approach to integrate various high-throughput data sets has let to the refinement of the genomic etiology of SCLC and to the identification of key biological processes, which might lead to novel therapeutic options for this deadly lung cancer subtype.

# Telomerase activation by genomic rearrangements in high risk neuroblastoma

Consortia SMOOSE/ SYSMED-NB

**Presenting Author: Matthias Fischer**

Martin Peifer (1,2), Falk Hertwig (2,3), Frederik Roels (2,3), Daniel Dreidax (4), Moritz Gartlgruber (4), Roopika Menon (5,6), Andrea Krämer (2,3), Frederik Sand (2), Johannes Heuckmann (6), Barbara Hero (3), Alexander Schramm (7), Johannes Schulte (8,9,10), Carl Herrmann (11), Roderick J O'Sullivan (12), Frank Westermann (4), Roman K Thomas (1,13), Matthias Fischer (2,3,14)

(1) Department of Translational Genomics, Center of Integrated Oncology Cologne–Bonn, Medical Faculty, University of Cologne (2) Center for Molecular Medicine Cologne (CMMC), University of Cologne (3) Department of Pediatric Oncology and Hematology, Medical Faculty, University Children's Hospital of Cologne (4) Division Neuroblastoma Genomics (B087), German Cancer Research Center, Heidelberg (5) Department of Prostate Cancer Research, Institute of Pathology, Center for Integrated Oncology Cologne-Bonn, University Hospital of Bonn (6) NEO New Oncology AG, Cologne (7) Department of Pediatric Oncology and Hematology, University Children's Hospital, Essen (8) Department of Pediatric Oncology and Hematology, Charité University Medical Center Berlin (9) German Cancer Consortium (DKTK), Berlin (10) German Cancer Research Center (DKFZ), Heidelberg (11) Cancer Regulatory Genomics Group, Division Theoretical Bioinformatics (B080), Heidelberg (12) Department of Pharmacology and Chemical Biology, University of Pittsburgh Cancer Institute (UPCI), Hillman Cancer Center, Pittsburgh, USA (13) Department of Pathology, University of Cologne (14) Max Planck Institute for Metabolism Research, Cologne

Background: Neuroblastoma is a pediatric tumor of the sympathetic nervous system with a broad range of clinical behavior, ranging from spontaneous regression to fatal progression. The genetic etiology and molecular mechanisms underlying these different phenotypes have remained largely elusive. Methods: We applied an integrated genomics approach combining whole genome sequencing, RNA sequencing, targeted sequencing, FISH analysis, and chromatin immunoprecipitation coupled to sequencing (ChIP-seq). Results: We discovered genomic rearreangements affecting a chromosomal region at 5p15.33 proximal of the telomerase reverse transcriptase (TERT) gene in 28/217 neuroblastomas (13%). These rearrangements occurred almost exclusively in high risk tumors lacking MYCN amplification (22/65 cases), and were strongly associated with poor patient outcome. Despite a large structural diversity of the rearrangements, they consistently induced massive upregulation of TERT expression. Using ChIP-seq analysis, we found that the rearrangements juxtapose the TERT locus to strong enhancer elements, resulting in massive epigenetic remodeling of the affected region. In the remaining high risk tumors, TERT expression was also upregulated in MYCN-amplified cases, while alternative lengthening of telomeres was present in high risk tumors without TERT or MYCN alterations. By contrast, telomere maintenance mechanisms were lacking in low risk tumors. Supporting a functional role of TERT, neuroblastoma cell lines bearing rearrangements or amplified MYCN exhibited both upregulated TERT expression and enzymatic telomerase activity. Conclusion: We show that remodeling of the genomic context by chromosomal rearrangements abrogates transcriptional TERT silencing in high risk neuroblastoma. Our data indicate that activation of telomere maintenance mechanisms is the central molecular event in high risk neuroblastoma, thus providing a mechanistic definition of this neuroblastoma subtype.

# Identifying telomere maintenance mechanisms in glioblastoma cell lines and primary tumor samples

Consortium CancerTelSys

**Presenting Author: Katharina Deeg**

Katharina Deeg (1), David Jones (2), Inn Chung (1) , Elke Pfaff (2), Stefan Pfister (2) and Karsten Rippe (1)

(1) Research Group Genome Organization & Function, DKFZ and BioQuant (2) Division of Pediatric Neurooncology, DKFZ

The life span of every eukaryotic cell is limited by a 'molecular clock', which is represented by the telomeres, repetitive DNA sequences that protect the ends of linear chromosomes. Like a countdown timer, the telomeres shorten during each round of cell division, eventually leading to the induction of senescence or apoptosis once the telomeres become too short. Thus, cancer cells depend on a telomere maintenance mechanism (TMM) for unlimited proliferation. This process frequently involves the activation of the reverse transcriptase telomerase. However, a significant fraction of tumors maintains their telomeres in the absence of telomerase by a pathway termed alternative lengthening of telomeres (ALT) that involves recombination and repair processes. ALT-positive tumors and cell lines are characterized by several molecular hallmarks, yet the mechanistic details of ALT remain poorly understood. Importantly, stratification of cancer patients according to the type of TMM that is active in the tumor provides valuable prognostic information in some tumor types and can impact treatment options. Thus, a better understanding of the ALT mechanism is needed as well as assays that reliably identify the active TMM in a clinical setting. We have performed a detailed analysis of TMMs in pediatric glioblastoma (pGBM) cell lines and tumors. This tumor entity is of particular interest as it has an unusual high prevalence of ALT. Yet, ALT-positive cell lines derived from pGBM were lacking up to now. Using a broad range of assays, we identified and characterized five ALT-positive pGBM cell lines. These cell lines provide valuable model systems to gain a better understanding of the ALT pathway and to evaluate novel ALT-targeted therapies in a preclinical setting. In addition, we were able to identify ALT in primary tumor samples using very low amounts of DNA. Given the fact that primary tumor material is limited, this finding will advance ALT identification in a clinical setting.

# Causal modeling of stroma-cancer cell communication

Demonstrator MMML-Demonstrators

**Presenting Author: Julia C. Engelmann**

Julia C. Engelmann (1), Claus Hellerbrand (2), Rainer Spang (1)

(1) Statistical Bioinformatics, University of Regensburg, Germany (2) Internal Medicine I, University Hospital Regensburg, Germany

Inter-cellular communication of stromal and cancer cells is well recognized to have a crucial role in carcinogenesis, tumor growth and cancer cell migration. Providing growth and survival factors, and increasing tumor cell motility by secreting proteolytic enzymes which loosen up the extracellular matrix are examples for stromal signals affecting cancer cells. Molecules involved in this inter-cellular communication are potential drug targets. To identify these systematically, we applied a systems level analysis combining experimental and computational approaches for studying inter-cellular communication via secreted gene products. Our approach builds on statistical methodology for causal analysis which consists of reverse network engineering followed by causal effect estimation using genome scale observational data. In the context of molecular interactions between hepatic stellate cells (HSC, a stromal cell type) and hepatocellular carcinoma (HCC) cells, we predicted causal effects of HSC secreted gene products on tumor (HCC) gene expression. The many cause-effect pairs were then condensed to a small set of stromal factors which together cause the majority of gene expression changes observed in HCC cells after exposure to the stromal secreted factors. The set of secreted stromal factors contained both known and unknown cancer promoting factors, including Hepatocyte Growth Factor (HGF), Placental Growth Factor (PGF) and Periostin (POSTN) as representatives of the former, and Pregnancy-Associated Plasma Protein A (PAPPA) as an example of the latter. We could show that PAPPA contributes to the activation of NFkB signaling in vitro. In clinical data, higher levels of PAPPA were linked to advanced stage HCC. In summary, this study demonstrates the potential of causal modeling in the identification of stromal signaling molecules influencing the cancer phenotype.

# Multiscale modelling of vascular dependent tumor growth in hepatocellular carcinoma (HCC) under therapy with transarterial chemoembolization (TACE)

Consortium Multiscale HCC

**Presenting Author: Michael Bitzer**

Holger Perfahl* 1, Marius Horger2, Nisar P. Malek3, Matthias Reuss1, Michael Bitzer3

1Stuttgart Research Center Systems Biology, University of Stuttgart, Stuttgart, Germany 2Diagnostic and Interventional Radiology, University Hospital Tuebingen, Tuebingen, Germany 3Internal Medicine I, University of Tuebingen, Tuebingen, Germany

Background and Aims: TACE is an established option in advanced HCC. Despite complete disruption of blood flow, a distinct number of surviving tumor cells are responsible for tumor regrowth. To investigate different parameters that determine TACE efficacy, a mathematical model was developed to study the evolution of vascular supply and angiogenesis. This model is informed, parameterized and directly validated using clinical data (43 patients). The aim was to improve TACE efficacy. Methods: Development of a 3-D multiscale model, coupling blood flow, angiogenesis, vascular remodelling, nutrient/growth factor transport, interactions between normal and tumour cells, and nutrient-dependent cell cycle dynamics. In 48 patients, volume perfusion CT was performed within 24 h before and after TACE with doxorubicin loaded beads (DEB) for 73 lesions. CT was repeated after 90 days. Response to TACE was classified as complete (no residual perfusion), partial (incomplete embolization) or no response. Results: The modeling, based on 73 TACE treated HCC lesions, simulates occlusion of tumor-supplying blood vessels by DEBs, leading to a local break down of the vascular system and induction of large hypoxic regions with a very low cancer cell survival. Released doxorubicin additionally targets cancer cells. The high degree of hypoxia and induced release of VEGF stimulates angiogenesis, with stepwise tumor revascularization and regrowth, which is dependent on several identified parameters. We also included patients with a second TACE, and defined relevant parameters that determine TACE outcome. Of note, already after two TACE cycles the tumor is subdivided into clusters, that should be considered in therapy. Conclusions: We have set up a simulation model using clinical data from 73 TACE treated HCC lesions in 43 patients to study TACE-induced hypoxia, necrosis and stimulation of angiogenesis. Based on these results an improvement of current TACE application strategies will be discussed.

# Dimerized EGFR-targeted protein formats of single-chain TNF-related apoptosis inducing ligand (TRAIL) are highly effective antitumor therapeutics

Demonstrator Melanoma sensitivity

**Presenting Author: Martin Siegemund**

Martin Siegemund1, Oliver Seifert1, Aline Plappert1, Sina Fellermeier1, Nadine Pollak1, Kristin Wahl2, Kirstin Hanak2, Arndt Vogel2, Andreas K. Nussler3, Daniele Lecis4, Pierfausto Seneci5, Doris Göttsch1, Sabine Münkel1, Heike Bantel2, Roland E. Kontermann1

1 Institute of Cell Biology and Immunology, University of Stuttgart, Allmandring 31, D-70569 Stuttgart, Germany

2 Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Carl-Neuberg-Str. 1, D-30625 Hannover, Germany

3 Department of Trauma Surgery, Eberhard Karls University Tübingen, Schnarrenbergstr. 95, D-72076 Tübingen, Germany

4 Department of Experimental Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Amadeo 42, 20133 Milano, Italy

5 Department of Chemistry, Università degli Studi di Milano, Via Golgi 19, 20133 Milano, Italy

Highly potent induction of apoptosis and superior tumor responses have been shown for TRAIL fusion proteins combining antibody-mediated targeting of tumor-associated antigens, e.g. EGFR, with a dimeric assembly of a single-chain (sc)TRAIL format. We incorporated those functions in the molecule Db-scTRAIL by non-covalent anti-EGFR diabody formation. In scFv-EHD2-scTRAIL, the EHD2 domain from IgE allowed covalent dimerization of scTRAIL while EGFR targeting was accomplished by scFv fusion. Db-scTRAIL exceeded the bioactivity of non-targeted monomeric scTRAIL ~100-fold in vitro with EC50 values of 2.7×10-12 M on EGFR+ Huh-7 hepatocarcinoma and 2.1×10-12 M on Colo205 colon carcinoma cells sensitized for apoptosis. ScFv-EHD2-scTRAIL showed in presence of bortezomib a > 200-fold increased bioactivity on Colo205 cells and a ~50-fold increase on NCI-H460 non-small lung cancer cells compared with scTRAIL, respectively. The crucial impact of a dimeric TRAIL status was proven by the higher potencies of either Db-scTRAIL on target-negative cells or non-targeted EHD2-scTRAIL on EGFR+ cells. Remarkably, both molecules remained strictly tumor selective, as evident from the lack of acute in vivo liver toxicity and good tolerance to repeated systemic applications in mouse models. The antitumor efficacies of tumor-targeted Db-scTRAIL and scFv-EHD2-scTRAIL in mouse xenograft models (Colo205) were superior to non-targeted scTRAIL formats, and overall tumor responses were clearly enhanced by co-treatment with bortezomib or small Smac peptidomimetics. Besides the target antigen-dependent induction of apoptosis, our dimeric scTRAIL formats provide additional benefits like down-regulation of EGF-induced EGFR autophosphorylation as shown for Db-scTRAIL or an improved pharmacokinetics in case of scFv-EHD2-scTRAIL. Our work demonstrates that cell surface targeting of dimeric scTRAIL fusion protein formats provides a favorable strategy to transform TRAIL into a striking antitumor molecule.

## The TIPC project: T-cell therapy In Pancreatic Cancer

Consortium PANC-STRAT

**Presenting Author: Rienk Offringa**

Isabel Poschke1, Michael Volkmar1, Oliver Strobel3, Thilo Hackert3, Nathalia Giese3, Markus Büchler3, Frank Bergmann4, Niels Halama5, Dirk Jäger5, Martin Sprick2, Andreas Trumpp2, Hanno Glimm6, Ugur Sahin7, Rienk Offringa1,3

(1) Div. Molecular Oncology of Gastrointestinal Tumors; (2) Div. Cancer Stem Cells, German Cancer Research Center, Heidelberg; (3) European Pancreas Center, Surgery Clinic, University of Heidelberg; (4) Institute for Pathology, University of Heidelberg; (5) Dept. Clinical Oncology; (6) Translational Oncology National Center for Tumor diseases, Heidelberg; (7) BioNTech Inc., Mainz; Germany

The objective of this project is to develop new immunotherapeutic treatment options for patients with pancreatic cancer, a disease marked by its highly metastatic nature, devastating recurrence rate and insensitivity to chemo and radiotherapies. Immunotherapeutic strategies have been left relatively unexplored for pancreatic cancer, due to the general belief that this is a poorly immunogenic tumor, which has been supported by the poor efficacy of checkpoint blockade in this indication. In contrast to this notion, our analysis of >100 resected primary tumor samples provided cumulative evidence for an anti-tumor T-cell immune response. Immunohistochemistry reveals prominent T-cell infiltrates in the majority (~ 70%) of tumor biopsies. These tumor-infiltrating lymphocytes (TILs) display an activated phenotype very similar to that of melanoma TILs, and can be effectively expanded ex vivo with protocols that are used to prepare T-cell batches for TIL-therapy in melanoma. Furthermore, next-generation T-cell receptor (TCR) sequencing of TIL and PBMC isolates from patients shows that the T-cell repertoire in the tumor is less diverse and comprises larger T-cell clones. Finally, in ~ 80% of tumor specimen, T-cell infiltration is accompanied by the presence of tertiary lymphoid structures that comprise T- and B-cell areas along with CD208+ and follicular dendritic cells. The latter two findings suggest that clonal expansion of T-cells takes place in the tumor microenvironment. Our current research focuses on the analysis of anti-tumor reactivity and antigen-specificity of the T-cell clones that are prominently enriched in the tumor (see also TIL-REP project). The tumor xenografts and genetics data provided by the PANC-STRAT consortium are important assets in this respect. Furthermore, we are developing powerful clinical approaches to harness this T-cell response by means of agonist immunostimulatory antibodies (ww.IACT-project.eu) and by the exploration of TIL therapy for the treatment of recurrent disease.

# Mutational dynamics between primary and relapsing neuroblastoma

Consortium SYSMED-NB

**Presenting Author: Alexander Schramm**

Alexander Schramm 1, Johannes Köster 2,17, Yassen Assenov 3, Kristina Althoff 1, Martin Peifer 4,5, Ellen Mahlow 1, Andrea Odersky 1, Daniela Beisser 2, Corinna Ernst 2, Anton G Henssen 1,17, Harald Stephan 1, Christopher Schröder 2, Lukas Heukamp 6,17, A

1 Pediatric Oncology and Hematology, University Children's Hospital Essen, University of Duisburg-Essen, Essen, Germany. 2 Genome Informatics, Institute of Human Genetics, University Hospital Essen, University of Duisburg-Essen, Essen, Germany. 3 Division of Epigenomics and Cancer Risk Factors, German Cancer Research Center (DKFZ), Heidelberg, Germany. 4 Department of Translational Genomics, University of Cologne, Cologne, Germany. 5 Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany. 6 NEO New Oncology, Cologne, Germany. 7 Pediatric Oncology and Hematology, University Children's Hospital, Cologne, Germany. 8 Cologne Center for Genomics, University of Cologne, Cologne, Germany. 9 Human Genetics, University Hospital Cologne, Cologne, Germany. 10 Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany. 11 Pediatric Oncology and Hematology, Charité University Medicine, Berlin, Germany. 12 Centre for Medical Genetics, Ghent University Hospital, Ghent, Belgium. 13 German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Heidelberg, Germany. 14 Computer Science, TU Dortmund, Dortmund, Germany. 15 Pediatric Oncology and Hematology, University Medicine Greifswald, Greifswald, Germany. 16 Neuroblastoma Genomics, B087, German Cancer Research Center (DKFZ), Heidelberg, Germany. 17 Present addresses: Center for Functional Cancer Epigenetics, Departments of Medical Oncology and Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA (J.K.), NEO New Oncology, Cologne, Germany, and Institute for Hematopathology, Hamburg, Germany (L.H.) and Memorial Sloan Kettering Cancer Center, New York, New York, USA (A.G.H.).

Neuroblastoma is a malignancy of the developing sympathetic nervous system that is often lethal when relapse occurs. We here used whole-exome sequencing, mRNA expression profiling, array CGH and DNA methylation analysis to characterize 16 paired samples at diagnosis and relapse from individuals with neuroblastoma. The mutational burden significantly increased in relapsing tumors, accompanied by altered mutational signatures and reduced subclonal heterogeneity. Global allele frequencies at relapse indicated clonal mutation selection during disease progression. Promoter methylation patterns were consistent over disease course and were patient specific. Recurrent alterations at relapse included mutations in the putative CHD5 neuroblastoma tumor suppressor, chromosome 9p losses, DOCK8 mutations, inactivating mutations in PTPN14 and a relapse-specific activity pattern for the PTPN14 target YAP. Recurrent new mutations in HRAS, KRAS and genes mediating cell-cell interaction in 13 of 16 relapse tumors indicate disturbances in signaling pathways mediating mesenchymal transition. Our data shed light on genetic alteration frequency, identity and evolution in neuroblastoma.


# Oral Presentations
# VIII ELSA on Systems Medicine

# Challenges of Big Data for Data Protection in Biomedical Research

**Presenting Author: Irene Schlünder**

TMF e.V Berlin

Using patient data in research raises data protection concerns, be the data derived from EHRs, clinical studies, biobanks, genetic databases, or other sources. Many issues become topics again, when various data sources are combined. Research on Big Data is increasingly happening in international data bases, but the legal framework remains national. EU Law provides for harmonization in Europe, internationally only „softlaw“ leads to common rules. The EU Data Protection Directive prohibits any processing of personal data, if it is not explicitly permitted for example by consent. But to define the research purpose in consent forms is often difficult in Big Data driven research. The dichotomy of data protection law - only personal and not anonymous data is protected – leads to the conclusion, that anonymization is the „magic bullet“ to get rid of data protection constraints. But there are some side-effects of anonymization: unlinked anonymization deprives the donor of the possibility to withdraw consent and makes feeding back information to patients impossible. In addition, regarding Big Data traditional anonymization methods might be inadequate, since they reduce or distort information that could be relevant for research. Moreover, they are getting weak to protect patients. Especially problematic is the anonymization of genetic data: although DNA sequences alone do not disclose the identity of an individual, they can contain enough information to single out a person. There is mounting evidence, that re-identification is constantly becoming easier. Therefore, consent will remain a key factor for complying with data protection law, so called “broad consent” is crucial for big data analysis. In addition, new methods are needed (e.g.: safe haven: data use only onsite, privacy preserving data mining). Will future data protection law support them?

# The ambivalent situation of BRCA mutation carriers. Transdisciplinary perspectives

## ELSA Project SYSKON

Foto: Ralf Rödel

**Presenting Authors:**
**Rita Schmutzler / Peter Dabrock**

University of Erlangen / University and University Clinics Cologne

BRCA1/2 mutations cause strongly elevated lifetime risks of developing breast and ovarian cancer and contribute to about 25% of the hereditary burden. In recent years, there has been an increasing interest in prophylactic mastectomy, partly due to the so-called 'Jolie-effect'.

In order to meet the increasingly complex risk situation, we identify relevant psycho-social factors for counselling to support non-directive and preference-sensitive decision making. There is a need for quaternary care centres for a) the provision of evidence-based preventive measures, b) the incorporation of narrative-based prevention, c) genotype-/phenotype correlations in light of genetic heterogeneity and d) the establishment of national networks and registries that will allow the acquisition of clinical data relevant for outcome measures of risk-adjusted preventive options.

The risk situation for BRCA1/2 mutation carriers implies considerable impacts for the health care system in general and the clinical setting in particular such as the reimbursement of and assignment of patients to certain preventive measures. We have noticed that especially the predictive potential of increasing data accumulation ('big data') challenges i. the relation between private and public health interests and ii. the blurred distinction between 'healthy' and 'ill'.

To achieve a better understanding of the basic terms 'healthy' and 'ill' due to the aforementioned risk situation, we extend the concept of 'healthy ill' known from the debates about genome-based medicine and social impact of modern biomedicine. Based on this model, we develop a new pattern integrating the ethical, psycho-social, legal and health-economical aspects concerning BRCA1/2 to provide benchmarks for a governance perspective on systems medicine in general.

# Do patients have a right to receive their genetic raw data from sequencing studies?

## ELSA Project DASYMED

**Presenting Authors:**
**Henrike Fleischer / Christoph Schickhardt**

Institut für Deutsches, Europäisches und Internationales Medizinrecht, Gesundheitsrecht und Bioethik der Universitäten Heidelberg und Mannheim (IMGB), National Center for Tumor Diseases (NCT)

Recently, several physicians and physician-scientists have been reporting patients and research participants requesting their genetic raw data after participating in genome or exome sequencing studies. Such requests raise several legal, ethical and practical questions. First, the normative question is addressed whether the distinction of research versus treatment context is relevant for the way we evaluate an individuals' request for their genetic data. We also need to differentiate the types of "raw data" potentially involved with respect to their informative value (somatic raw data, somatic variants, germline raw data). Second, from a legal perspective, according to the German data protection law an individual has the right to obtain information about his or her data stored, and the German Civil Code provides the right for patients to access their medical records. However, a major legal challenge consists in the question whether the German Genetic Diagnostics Act (GenDG) and its principles exclude the direct release of raw data to patients since the GenDG defines high standards concerning counseling and informing patients with regard to results of genetic testing. In particular, results of genetic testing shall only be disclosed by the physician in charge. We will argue though that the GenDG does not prohibit the release of genetic raw data to patients. However, in the research context the right to obtain information about one's personal data must be balanced with the freedom of research. Our ethical analysis basically backs the legal interpretation: Respect for patients and research participants as autonomous agents and emancipated partners implies the right to informational self-determination, which in turn includes a basic right of access to personal genetic raw data stored by third parties. Therefore, we propose a three step procedure for institutions to respond to patients' requests to obtain raw data.


# Poster Presentations

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

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| 102 | P-III-4, PW | Caroline Prell-Schicker | Transcriptional regulation of HDAC9 by rs2107595 – the lead SNP in METASTROKE | Consortium e:AtheroSysMed |
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| 104 | P-III-6 | Christian Roth | Prediction of target genes for regulatory SNPs identified in GWAS | Consortium e:AtheroSysMed |
| 105 | P-III-7, PW | Xue Li | Macrophages are crucial for cardiac regeneration in zebrafish | Junior Research Alliance DeCaRe |
| 106 | P-III-8 | Harald Seitz | Quality Management of Antibodies during Assay Development | Consortium e:Kid |
| 107 | P-III-9, PW | Renate Schnabel | Genetic Risk Score for Atrial Fibrillation in the General Population | Junior Research Alliance symAtrial |
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| 120 | P-IV-7, PW | Philippe Lucarelli | Analysis of the TRAIL-induced apoptosis and ERK-MAPK signal transduction pathways in melanoma cell lines by a probabilistic Boolean network approach | Demonstrator Melanoma sensitivity |
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| 122 | P-IV-10, PW | Michael Rauer | Toward modeling Transcription factor activity in cancer | Junior Research Alliance MILES |
| 123 | P-IV-11, PW | Stefan Albert | Stochastic spike train models capture temporal patterns in perceptual responses to a bistable stimulus | Junior Research Alliance PsychoSys |
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| 129 | P-V-3 | Michael Bitzer/ Claudia Zwingmann | Systems Biology Supports Multiscale Analysis of Imaging, Omics and Clinical Data to Improve Diagnosis and Therapy of HCCs (MultiscaleHCC) | Consortium Multiscale HCC |
| 130 | P-V-4 | Martin R. Sprick | CYP3A5 mediates resistance to small molecule inhibitors in a subtype of pancreatic ductal adenocarcinoma | Consortium PANC-STRAT |
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| 135 | P-V-9, PW | Hedwig Deubzer | The MCM complex is a critical node in the miR-183 signaling network of high-risk neuroblastoma cells | Consortium SYSMED-NB |
| 136 | P-V-10 | Birgit Luber and Dieter Maier | Identification of predictive response and resistance factors to targeted therapy in gastric cancer using a systems medicine approach | Consortium SYS-Stomach |
| 137 | P-V-11 | Ivonne Haffner | Clinical validation of response and resistance factor candidates to targeted therapy in gastric cancer (GC) | Consortium SYS-Stomach |
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| 141 | P-V-15 | Markus Rehm | Clinical application of a systems model of apoptosis execution as a prognostic tool in stage 3 colorectal cancer | Demonstrator Melanoma sensitivity |
| 142 | P-V-16, PW | Isabel Poschke | TIL-REP Junior Consortium - dynamics of the tumor infiltrating lymphocyte repertoire in melanoma and pancreatic cancer | Junior Research Alliance TIL-REP |
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| 148 | P-VI-2 | Jana Strohmaier | Validity of a self-rating questionnaire for major depressive disorder: Comparison with clinical interview data | Consortium IntegraMent |
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| 158 | P-VII-2 | Peter Ahnert | Dynamical modelling of the murine immune response to pneumococcal lung infection with and without antibiotic treatment | Consortium CAPSyS |
| 159 | P-VII-3 | Peter Ahnert | Operationalization of Disease Severity for Community Acquired Pneumonia of hospitalized Patients | Consortium CAPSyS |
| 160 | P-VII-4 | Benjamin JD Weist | Concerted T-cell activity against early and late BKV-antigens is necessary for viral clearance | Consortium e:Kid |
| 161 | P-VII-5 | Alexey Uvarovskii | A modeling framework for early stages in tertiary lymphoid organ formation after renal transplantation | Consortium SYSIMIT |
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| 165 | P-VII-9 | Ateequr Rehmann | Biological therapies and intestinal microbiota: A longitudinal study in diverse disease phenotype | Consortium SysINFLAME |
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| 178 | P-VIII-7 | Pauline Mantell, Marc Jannes | Systems Medicine in the Prevention of Mental Disorders – A legitimate Approach? | ELSA SysKomp |
| 179 | P-VIII-8 | Friedhelm Meier | SYSKON. Re-configuration of health and disease. Ethical, psychosocial, legal and health economic challenges of systems medicine: The case of hereditary breast cancer. | ELSA SYSKON |

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# Poster Presentations
# I Epigenetics & Transcriptomics

# Identifying regulators of the telomerase employing Mixed Integer Linear Programming approaches

Consortium CancerTelSys

**Presenting Author: Alexandra Poos**

Alexandra Poos (1,2,3), Marcus Oswald (1,2), Roland Eils (3,4), Karsten Rippe (5) and Rainer König (1,2,3)

(1) Integrated Research and Treatment Center, Center for Sepsis Control and Care (CSCC), Jena University Hospital, D-07747 Jena, Erlanger Allee 101, Germany (2) Network Modeling, Leibniz Institute for Natural Product Research and Infection Biology - Hans Knöll Institute Jena, Beutenbergstrasse 11a, 07745 Jena, Germany. (3) Theoretical Bioinformatics, German Cancer Research Center, INF 580, 69121 Heidelberg, Germany (4) Department of Bioinformatics and Functional Genomics, Institute of Pharmacy and Molecular Biotechnology, and Bioquant, University of Heidelberg, Im Neuenheimer Feld 267, 69120 Heidelberg, Germany (5) German Cancer Research Center (DKFZ) and BioQuant, Research Group Genome Organization and Function, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany

Telomeres are nucleoprotein structures at the ends of the eukaryotic chromosomes protecting them against fusion, degradation and unwanted double-strand break repair mechanisms. The length and structure of telomeres is tightly controlled. Telomeric DNA is composed of repetitive sequences and is synthesized by the reverse transcriptase telomerase. While unicellular organisms like yeast constitutively express telomerase, the majority of human cells lacks telomerase activity. Thus, telomeres shorten gradually with each cell division. The accumulation of critically short telomeres leads to replicative senescence or apoptosis. Consequently, 85-90% of tumours re-express telomerase to maintain their telomeres and proliferate indefinitely. Thus, a better understanding of the telomere maintenance mechanisms is important for biomedical research, in particular for ageing and cancer research. We aim to elucidate regulatory mechanisms of telomerase expression, and developed the R package MIPRP based on Mixed Integer Linear Programming. This approach involves machine learning methods to identify the regulation of the telomerase genes. As a case study, we applied our tool to expression data of Saccharomyces cerevisiae. Furthermore, we applied our method to RNA-Seq data of prostate cancer patients from The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC). For this, known transcription factor to target gene interactions were assembled from different databases comprising MetaCore, Encode and CheA. By investigating the distinct regulation of the telomerase reverse transcriptase (TERT) in tumour samples with high TERT expression, the androgen receptor (AR) as well as the MYC-associated zinc finger protein (MAZ) were identified as regulators of TERT expression in prostate cancer.

# The multifaceted function of histone Lysine-Specific Demethylase (LSD1) in non-small cell lung cancer

Consortium SMOOSE

**Presenting Author: So-Young Lim**

So-Young Lim1,2, Iris Macheleidt1,2, Michael Gentz1,2, Roland Schüle3, Michal Schweiger4, Margarete Odenthal1,2, and Reinhard Büttner1,2

1Institut of Pathology, University Hospital of Cologne, Kerpener Strasse 62, 50294 Cologne, Germany, 2The Center for Molecular Medicine Cologne (CMMC), Robert-Koch-Strasse 21, 50931, Cologne, Germany 3Urologische Klinik und Zentrale Klinische Forschung, Klinikum der Universität Freiburg, Breisacherstrasse 66, 79106 Freiburg, Germany, 4Funtional Epigenomics, Universtiy of Cologne, Weyertal 115b 50931 Cologne, Germany

KRAS mutations occurring in approximately 25% of non-small cell lung cancer (NSCLC) have long been considered undruggable and account for the resistance to the EGFR inhibitors. Therefore, new therapies NSCLC with KRAS mutation are urgently needed. The histone H3K4 and H3K9 di/mono-demethylase LSD1 is a key epigenetic writer, aberrantly upregulated in many cancer types, including NSCLC. In order to understand the functional role of LSD1 in the progression of NSCLC, we established shRNA-mediated, stable LSD1 knock-down cell line using KRAS mutated A549 lung adenocarcinoma cells. LSD1 knock-down led to retardation of cell growth and decrease in cell invasion and self-renewal capability. Moreover, LSD1 inhibition sensitized the EGFR inhibitor resistant tumor cells to erlotinib treatment. LSD1 knock-down in A549 cell resulted in a dramatic change in gene transcriptome profile, as determined by RNA-Seq. Interestingly, target downstream genes of lung tissue-specific transcription factors such as FOXA1 and CEBPB were affected by LSD1 knock-down, indicating the potential role of LSD1, not only in the oncogenic signal pathways but also in the differentiation of lung epithelial cell-lineage. In addition, GSEA analysis revealed that genes involved in the KRAS signature were significantly affected upon LSD1 knock-down especially in KRAS mutated A549 cells. This implicates the possible interference of oncogenic KRAS signal pathway by LSD1 inhibition. Further studies using the mouse model of KRAS mutation-driven lung cancer will reveal the therapeutic potential of the LSD1 inhibition for the KRAS mutant NSCLC as a monotherapy or a combination therapy with other cancer drugs.

# Transcriptome profiling of human inflammatory bowel disease

Consortium SysINFLAME

**Presenting Author: Raheleh Sheibani-Tezerji**

Raheleh Sheibani-Tezerji1, Matthias Barann1, Robert Häsler1, Berenice Brandt2, Konrad Aden1,2, Stefan Schreiber1,2 and Philip Rosenstiel1

1 Institute of Clinical Molecular Biology, Christian-Albrechts-University and University Hospital Schleswig-Holstein, Campus Kiel, 24105 Kiel, Germany 2 First Medical Department, Christian-Albrechts-University and University Hospital Schleswig-Holstein, Campus Kiel, 24105 Kiel, Germany

The term inflammatory bowel disease (IBD) relates to a group of chronic relapsing-remitting inflammatory diseases, which affect all or parts of the digestive tract. It can be sub-classified into two major forms, Crohn's disease (CD) and ulcerative colitis (UC). High-throughput RNA-seq based gene expression profiling experiments have resulted in a gamut of information on regulatory abnormalities in the transcriptome such as generation of new transcriptionaly active regions and alternative splicing. The alternative splicing machinery creates diverse RNA isoforms from a single gene that result in numerous protein isoforms with varied functionalities. Several existing reports have linked this mechanism with cancer progression and other diseases. Although a plethora of information on gene expression in IBD is now available, the actual role of different gene products or proteins during the pathogenic development of IBD is still lacking. In the present study, whole transcriptome analysis of 63 samples comprising 19 CD, 17 UD, 15 disease control and 12 healthy control samples from 41 persons was performed. Differentially expressed genes and exons were estimated and alternative splicing events were reconstructed by combining exon-level analyses and transcript-level estimations. We identified differentially expressed genes and differential alternative splicing specific to the disease and tissue type. The numbers of alternative splicing genes between CD and UC samples were found significantly different and thus indicated different roles of splicing in both cases. Overall, our study catalogues a comprehensive survey of CD and UC transcriptomes and isoforms highlighting the complexity of regulatory changes during inflammatory bowel disease as well as common features and genetic overlaps between CD and UC.


# Poster Presentations
# III Cardiovascular Diseases

# Functional evaluation of rare GUCY1A3 variants in patients affected by premature myocardial infarction

Consortium e:AtheroSysMed

**Presenting Author: Jana Wobst**

Jana Wobst1, Thorsten Kessler1, Tan An Dang1, Simon von Ameln1, Stephanie Tennstedt2, Christian Hengstenberg1,3, Jeanette Erdmann2,4, Heribert Schunkert1,3

1 Klinik für Herz- und Kreislauferkrankungen, Deutsches Herzzentrum München, Technische Universtität München, Munich, Germany 2 Institut für Integrative und Experimentelle Genomik, Universität zu Lübeck, Germany 3 Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK) e.V., partner site Munich Heart Alliance (MHA), Munich, Germany 4 Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK) e.V., partner site Hamburg/Kiel/Lübeck, Lübeck, Germany

Myocardial infarction (MI) is the main complication of coronary artery disease (CAD). Recently, a locus tagging the GUCY1A3 gene has been shown to be genome-wide significantly associated with CAD[1]. GUCY1A3 encodes the α1 subunit of the soluble guanylyl cyclase (sGC), a heterodimer composed of α1 and β1 subunits. Upon stimulation with nitric oxide (NO) the sGC produces cGMP, a second messenger mediating e.g. smooth muscle relaxation and inhibition of platelet aggregation. Using whole-exome sequencing, our group also identified nine rare variants in the coding sequence of GUCY1A3 associated with CAD/MI[2]. We aimed to investigate the functional implication of these rare variants regarding protein levels, dimerization capability and enzymatic activity. Effects on protein level were investigated by Western blot analysis after overexpression of the variants in HEK cells. p.Gly537Arg exhibited significantly decreased protein levels compared to wild type α1. The amount of β1 correlated with those of α1 in all cases. We demonstrated that inhibition of the proteasome with Bortezomib didn't change the amount of p.Gly537Arg pointing to an effect on RNA level. qPCR analysis revealed almost 50 % decrease for p.Gly537Arg mRNA compared to wild type mRNA. All α1 variants, except for p.Leu163Phefs*24, dimerized with the β1 subunit, as shown by co-immunoprecipitation. sGC enzymatic activity was assessed by measuring cGMP in a radioimmunoassay after stimulating overexpressed HEK cells with NO for various time points. After 2 min of stimulation five of the variants demonstrated significantly decreased cGMP production compared to wild type α1. Interestingly, the addition of BAY41 lead to a rescue of impaired enzymatic activity in two of the variants (p.Ile571Val and p.Val587Ile). We identified nine rare variants in the coding sequence of the GUCY1A3 gene and demonstrated that these mutations may lead to altered protein levels as well as diminished activity. As both mechanisms in the end influence the capacity of cGMP formation, this appears to be a possible mechanism for GUCY1A3 leading atherosclerosis and MI. 1. CARDIoGRAMplusC4D, Deloukas P, Kanoni S et al: Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet 2013, 45(1):25-33. 2. Erdmann J, Stark K, Esslinger UB et al: Dysfunctional nitric oxide signalling increases risk of myocardial infarction. Nature 2013, 504(7480):432-436.

# In-silico Prediction of Causal Coronary Artery Disease Genes

Consortium e:AtheroSysmed

**Presenting Author: Benedikt Reiz**

Benedikt Reiz1,2, Ingrid Brænne1,2, Mariana Kleinecke1,2, Jeanette Erdmann1,2, Heribert Schunkert3,4

1Institut für Integrative und Experimentelle Genomik, Universität zu Lübeck, 23562 Lübeck, Germany; 2DZHK (German Research Centre for Cardiovascular Research), partner site Hamburg/Lübeck/Kiel, 23562 Lübeck, Germany; 3Deutsches Herzzentrum München, Technische Universität München, 80636 München, Germany ; 4DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, 80636 Munich, Germany

Background: To date, we have identified 202 significant and suggestive coronary artery disease loci (CAD) through genome-wide association studies (GWAS). Here, we report an extensive bioinformatics analysis to predict the causal genes underlying the reported CAD loci. Methods and results: We annotated each GWAS locus with respect to protein-altering SNPs, association with gene expression and altered miRNA binding sites. In addition, we used the publicly available ENCODE dataset to identify SNPs within regulatory regions of the genome, such as enhancer and promoter sites. Consistent with previous findings, we found that most CAD-loci lie in non-coding regions. Around half of the loci affect gene expression robustly, 2/3 overlap promoter regions and nearly all loci can be linked to other regulatory regions of the genome. In contrast, only a small percentage (5%) of SNPs affects protein coding. Comparing our in-silico gene annotation with the genes previously assigned to the loci, we found that a substantial number of genes differ. Indeed, we identify around 100 genes not linked with CAD before. Conclusion: Our results significantly revise the list of potential causal CAD genes underlying the genome-wide association signal and might help to shed new light on the genetic mechanisms of CAD.

# CAD-associated gene regulation through SNPs in micro-RNA binding sites

Consortium e:AtheroSysMed

**Presenting Author: Goekcen Eraslan**

Goekcen Eraslan, Nikola S. Mueller, Fabian J. Theis

Goekcen Eraslan, Nikola S. Mueller, Fabian J. Theis: Institute of Computational Biology, Helmholtz Zentrum München, Neuherberg, Germany Fabian J. Theis: Department of Mathematics, Technische Universität München, Garching, Germany

MicroRNAs (miRNAs) are small non-coding RNAs which play an important role in post-transcriptional gene regulation through silencing the expression of messenger RNAs (mRNAs). Dysregulation of miRNA is associated to various diseases including cancer. There is also evidence of various genes involved in heart diseases are regulated by miRNAs. Furthermore, heart disease risk loci in regulatory elements have been reported in the literature. However, the role of SNP-mediated miRNA dysregulation in the pathogenesis of heart diseases is unclear. To investigate the effects of miRNA dysregulation to heart diseases, we investigate Coronary artery disease (CAD) in the e:AtheroSysMed consortium. In particular, the occurrence of CAD-associated risk SNPs that are located in miRNA-mRNA binding sites and the risk SNPs that may impair mRNA-miRNA binding are identified. Here we propose a bioinformatics pipeline to look up the LD proxies of given risk SNPs and to find the SNPs localized in miRNA binding sites using the miRNA binding site information from three different databases. 416 CAD risk SNPs are first imputed with LD information from 1000G project, and among those 8776 SNPs including the LD proxies, 110 SNPs are identified in miRNA binding sites. The eQTL dataset derived from monocytes and macrophages by Deutschen Herzzentrum München (DHM) which is utilized in our analysis supports that risk SNPs in miRNA binding sites affect the expression of the miRNA target genes. Additionally, by randomly positioning genomic intervals over 3'UTR regions and determining overlapping SNPs, we calculated an empirical p-value which shows that the number of SNPs in miRNA binding sites is more than expected by chance. Our results demonstrate how miRNA dysregulation is likely to be involved in the pathogenesis of CAD. We are planning to share the pipeline with a web interface which will enable researchers to interrogate associations between SNPs of interest and miRNA binding sites.

# Transcriptional regulation of HDAC9 by rs2107595 – the lead SNP in METASTROKE

Consortium e:AtheroSysMed

**Presenting Author: Caroline Prell-Schicker**

Caroline Prell-Schicker (1), Tar Viturawong (2), Matthias Prestel (1), Matthias Mann (2), Christof Haffner (1), Martin Dichgans (1)

(1) Institute for Stroke and Dementia Research (ISD), Ludwig-Maximilians-University, 81377 Munich, Germany. (2) Max-Planck-Institute for Biochemistry, 82152 Martinsried, Germany

# Mechanistic insights from the PDE5A locus in coronary disease risk

Consortium e:AtheroSysMed

**Presenting Author: Tan An Dang**

Tan A Dang1, Thorsten Kessler1, Manuel Lehm2, Simon v. Ameln1, Jana Wobst1, Matthias Prestel2, Redouane Aherrahrou3, Ingrid Braenne3, Christian Hengstenberg1,4, Martin Dichgans2, Jeanette Erdmannn3,5, Heribert Schunkert1,4

1 Deutsches Herzzentrum München, Klinik für Herz- und Kreislauferkrankungen, Technische Universität München, Munich, Germany 2 Institut für Schlaganfall- und Demenzforschung, Ludwig-Maximilians-Universität München, Munich, Germany 3 Universität zu Lübeck, Institut für Integrative und Experimentelle Genomik, Lübeck, Germany 4 Deutsches Zentrum für Herz- und Kreislaufforschung (DZHK) e.V., partner site Munich Heart Alliance (MHA), Munich, Germany 5 Deutsches Zentrum für Herz- und Kreislaufforschung (DZHK) e.V., partner site Hamburg/Kiel/Lübeck, Lübeck, Germany

Performing whole-exome sequencing, our group has identified a mutation in the phosphodiesterase 5A gene (PDE5A) in a family suffering from premature coronary artery disease (CAD) and myocardial infarction (MI). Mutations in proteins involved the cGMP-signalling cascade have already been shown to play a crucial role in CAD and MI risk [1]. Here, we aimed to investigate the molecular mechanisms of this particular mutation on cellular and molecular phenotypes. PDE5A encodes for three distinct isoforms, PDE5A1, PDE5A2, and PDE5A3, which degrade cGMP, a secondary messenger important for thrombocyte inhibition and smooth muscle relaxation. The mutation is located in the first exon of PDE5A2 leading to a premature stop codon, and the first intron of PDE5A1 and PDE5A3, which is described as an alternative promoter site [2]. Reporter gene analysis of the alternative promoter site in HEK293 cells by luciferase assay revealed a significant increase in promoter activity with the mutated allele (40%). Underpinning these findings, stable isotope labelling by amino acids in cell culture (SILAC) analysis in HeLa S3 nuclear lysates showed differential binding of the transcription factor ZFX to the major allele. Furthermore, overexpression experiments with PDE5A2 constructs carrying the mutation did not show a loss of transcript as expected by the premature stop codon but revealed the expression of a N-terminally truncated PDE5A2 isoform. cGMP radioimmuno assays (RIA) confirmed the activity of the truncated PDE5A2 isoform. We demonstrated an increased promoter activity of the mutated PDE5A allele, which could be mediated by differential binding of the transcription factor ZFX to the major allele. Increased promoter activity might lead to enhanced expression of the PDE5A isoforms, which has been demonstrated by the current studies. Moreover, since the N-terminal of PDE5A is important for the regulation of its catalytic activity by the GAF-domains, we hypothesize that the mutation also alters the functionality of the GAF domains leading to impaired cGMP binding and processing. Overall, our results point towards a gain of function mutation in PDE5A associated with CAD and MI.
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# Prediction of target genes for regulatory SNPs identified in GWAS

Consortium e:AtheroSysMed

**Presenting Author: Christian Roth**

Christian Roth and Johannes Soeding

Max Planck Institute for Biophysical Chemistry, 37077 Goettingen

Recent studies have shown that the great majority of disease-associated single-nucleotide polymorphisms (SNPs) are located in non-coding regulatory regions of the human genome. These SNPs alter the expression of a target gene, and thereby influence disease risk. To make progress in understanding the origins of complex diseases such as atherosclerosis it is critical to identify the target genes of regulatory SNPs for the many potentially causal disease--associated SNPs found in GWA studies. There is now increasing evidence that regulatory interactions can be precisely targeted over many 100 kbp. Therefore the common strategy of choosing the nearest gene will often fail to identify the true target genes. High-throughput experiments like DNAse-seq and 3C-based methods were developed to predict regulator gene interactions genome-wide. However these methods on their own currently either lack throughput or resolution to allow us to predict target genes. Here we propose a Bayesian statistical approach that combines correlations between DNAse accessibility and gene expression, genomic distance, and high resolution HiC interaction data in order to improve the predictions of regulator-gene interactions.

# Macrophages are crucial for cardiac regeneration in zebrafish

Junior Research Alliance DeCaRe

**Presenting Author: Xue Li**

Xue Li a,b, Hagen Klett a,c, Melanie Börries a,c, Florian Leuschner a,b, David Hassel a,b

aDeCaRe Junior-Consortium bUniversity Hospital Heidelberg, Internal Medicine III, Department of Cardiology, Angiology and Pneumology cSystems Biology of the Cellular Microenvironment Group, IMMZ, ALU, Freiburg; German Cancer Consortium (DKTK),Freiburg; German Cancer Research Center, Heidelberg

Myocardial infarction is one of the most frequent causes of death all over the world. Over 250,000 people incur a heart attack in Germany every year which underlines not only its socio economic relevance. During the past years the inflammatory response triggered by ischemic cell death came into focus of cardiovascular research. In the mammalian adult heart, the immune system facilitates scar formation, which repairs damaged myocardium but compromises cardiac function. However, zebrafish are able to fully regenerate their hearts after injury even in adults, leaving no trace of wound behind. Time-laps imaging of transgenic lines with fluorescently labeled neutrophils and macrophages demonstrated a rapid and transient initial neutrophilic response and a subsequent macrophages recruitment to the injured heart. We obtained a detailed migratory time-course that revealed conserved elements of the inflammatory cell response similar to that in mammals. We next selectively ablated macrophages to asses their requirement for cardiac regeneration. We found that ablation severely impaired regeneration and led to massive scar formation. While proliferation of dedifferentiating cardiomyocytes was not affected, we found that survival of newly generated myocytes was significantly reduced. Further, we observed that the injured region of the heart remained devoid of myocardial cells. Transcriptome data during regeneration demonstrated upregulation of genes involved in chemotaxis and migration, including migration-inducing chemokines, were induced when macrophages accumulate in the injured heart. Using in vitro migration experiments, we can demonstrate that the supernatant of activated macrophages is sufficient to induce directed migration of neonatal rat cardiomyocytes. Hence, we hypothesize that macrophages secrete signals that are essential for cardiomyocyte survival and that guide newly formed cardiomyocytes towards the injury site thereby reconstructing the injured heard and ultimately restoring heart function.

# Quality Management of Antibodies during Assay Development

Consortium e:Kid

**Presenting Author: Harald Seitz**

M.Sc. S. Schumacher and Dr. H. Seitz

Fraunhofer Institute for Cell Therapy and Immunology, Branch Bioanalytics and Bioprocesses, Am Muehlenberg 13, 14476 Potsdam

Objective: The aim of the study was to develop a multiplex immunoassay on a miniaturized platform for drug abuse in human sera. We chose nine different drugs as panel to start with. During the development process each reagent undergoes a stringent quality control e.g. antibodies used has to be validated with at least 2 independent methods. Methods: Western Blot analysis and ELISA were performed to test antibodies for specificity and selectivity against the selected drugs and human sera. A competitive ELISA was established allowing the quantification of the drugs in sera. Appropriate controls were included for background subtraction and determination of unspecific signals. The established assay will be transferred onto a miniaturized platform allowing a quantification of the drugs in a flexible and mobile device. Results and Discussion: For 4 out of 9 selected drugs specific antibodies could be obtained and a competitive ELISA established for quantification. Validated antibodies are characterized by no cross-reactivity to serum and no unspecific binding to other compounds or drugs. Serum samples with spiked drugs or samples from the LKA Berlin were analyzed and gave results comparable to established methods like GC-MS. Each sample was performed in triplicates and each experiment was done twice at least. Limits of quantification meet the requirements of the GTFCh. No cross-reactivity or matrix effects were observed with the validated antibodies. First multiplex and spotting experiments were done with a satisfying result. Conclusion: The presented approach enables a sensitive and reliable detection method for drug abuse. The validation studies are continued for the remaining drugs.

Key words: Immunoassay; serum; multiplex; validation; ELISA

# Genetic Risk Score for Atrial Fibrillation in the General Population

Junior Research Alliance symAtrial

**Presenting Author: Renate Schnabel**

Renate B. Schnabel 1, 2, Francisco M. Ojeda 1,2, Julia Krause 1,2, Markus Scheinhardt 3, Nargiz Rzayeva 1,2, Daniela Börnigen 1,2, Christian Müller 1,2, Matthias Heinig 4, Arne Schillert 3, Tanja Zeller 1,2

Clinic for General and Interventional Cardiology, University Heart Center Hamburg, Hamburg, 20246, Germany 2. German Center for Cardiovascular Research (DZHK e.V.), partner site Hamburg, Lübeck, Kiel, 20246, Germany 3. Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, Universitätsklinikum Schleswig-Holstein, Lübeck, Germany 4. Institute of Computational Biology, Deutsches Forschungszentrum für Gesundheit und Umwelt, Helmholtz Zentrum München, 85764 Neuherberg, Germany

Background: Atrial fibrillation (AF) is the most common arrhythmia in the general population. It has a heritable component. The value of genetic information from single nucleotide polymorphisms identified by genome-wide association studies (GWAS) in addition to classical risk factors remains little investigated. Methods and Results: In N=4096 individuals, 51% males of the population-based Gutenberg Health Study we examined 25 replicated genetic loci from GWAS for AF with one SNP representing each locus. We built a genetic risk score for prevalent AF (N=127) including age and classical risk factors from a recently published risk predication algorithm (height, weight, systolic and diastolic blood pressure, hypertension medication, current smoking, diabetes, heart failure, myocardial infarction). To account for possible batch effects in our genetic data we used the first batch as training (N = 2958) and the second batch as validation set (N = 1138). Logistic ridge regression for AF, which shrinks the coefficients toward zero, was used to combine the classical risk factors and genetic data. A ridge model consisting only of risk factors was also considered. According to a random forest for AF, age, height, weight and blood pressure were the most important predictors. rs6843083 was the top SNP according to this ranking. The discrimination of the model was not improved significantly (area under the curve for the clinical model 0.844 (95% confidence interval (CI) 0.777 to 0.91 versus area under the curve including all SNPs 0.847 (95% CI 0.777 to 0.917). No signs of model miscalibration were found for the genetic risk score (calibration-in-the-large -0.02 (95% CI -0.403 to 0.327). Conclusions: Genetic information from 25 SNPs identified in genome-wide association studies improved the association model of classical risk factors with AF only to a small extent, which may not be of clinical relevance. Whether additional genetic information enhances risk prediction models needs to be shown.

# Preparing Gene Expression Data for Large-scale Longitudinal Gene Expression Analysis of Atrial Fibrillation and Related Traits

Junior Research Alliance symAtrial

**Presenting Author: Arne Schillert**

Christian Müller1,2, Markus Scheinhardt3, Caroline Röthemeier1, David-Alexandre Trégouët4,5,6, Carole Proust4,5,6, Harald Binder7, Norbert Pfeiffer8, Manfred Beutel9, Karl J Lackner10,11, Renate B Schnabel2,3, Laurence Tiret4,5,6, Philipp S Wild11,12,13, Stefan Blankenberg2,3, Andreas Ziegler 2,3,14 Tanja Zeller1,2, Arne Schillert2,3,

1. Clinic for General and Interventional Cardiology, University Heart Center Hamburg, Hamburg 2. German Center for Cardiovascular Research (DZHK e.V.), partner site Hamburg, Lübeck, Kiel 3. Institute of Medical Biometry and Statistics, University Hospital Schleswig-Holstein, Campus Lübeck, Universität zu Lübeck 4. Institut National de la Santé et de la Recherche Médicale (INSERM), Unité Mixte de Recherche(UMR) enSanté 1166,Paris, France 5. Institute for Cardiometabolism and Nutrition (ICAN), Paris, France 6. Sorbonne Universités, Université Pierre et Marie Curie, UMR_S1166, Team Genomic & Pathophysiology of Cardiovascular Diseases, Paris, France 7. Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at the University Medical Center of the Johannes Gutenberg University Mainz. 8. Experimental Ophthalmology, Department of Ophthalmology, University Medical Center of the Johannes Gutenberg University, Mainz. 9. Department of Psychosomatic Medicine and Psychotherapy, University Medical Center of the Johannes Gutenberg-University Mazi 10. Institute for Clinical Chemistry and Laboratory Medicine, University Medical Center Mainz. 11.German Center for Cardiovascular Research (DZHK e.V.), partner site Rhine Main, Mainz 1Preventive Cardiology and Preventive Medicine, Department of Medicine II, University Medical Center Mainz 13. Center for Thrombosis and Hemostasis, University Medical Center Mainz 14. Center for Clinical Trials, University of Lübeck

Longitudinal gene expression analysis of atrial fibrillation (AF) and related electrocardiography traits may help to uncover important molecular mechanisms related to AF. Technical variation plays an important role in microarray-based gene expression studies, and batch effects explain a large proportion of this variation. therefore It is mandatory to reduce technical variation while maintaining biological variability. In this study, we aimed at (1) identifying a suitable method for batch effect removal in a large study of microarray-based longitudinal gene expression, and (2) applying this method to prepare the dataset for a subsequent analysis of AF related traits. Monocytic gene expression was measured in 1,092 participants of the Gutenberg Health Study (GHS) at baseline and 5-year follow-up. Replicates of selected samples were measured at both time points to identify technical variability. Deming regression, Passing-Bablok regression, linear mixed models and non-linear models as well as quantile normalization plus ComBat were applied to eliminate batch effects between replicates. Technical variation between batches was evaluated by principal component analysis. Associations between body mass index and transcriptomes were calculated before and after batch removal. Results from association analyses were compared to evaluate maintenance of biological variability. Quantile normalization, separately performed for baseline and follow-up data, combined with ComBat successfully removed batch effects and maintained biological variability while all other methods failed. Quantile normalization plus ComBat therefore appears to be a valuable approach for batch correction in longitudinal gene expression data. Subsequently, the dataset will be used to screen for AF related candidate genes by longitudinal gene expression analyses.

# SPNS2 Function Is Essential For Heart Chamber Specification In Zebrafish

Junior Research Alliance SYMBOL-HF

**Presenting Author: Daniela Asam**

Daniela Asam, Eva Patzel, Wolfgang Rottbauer, Steffen Just

University Hospital of Ulm Internal Medicine II Molecular Cardiology Albert-Einstein-Allee 23 89081 Ulm

Windbeutel (wil) is a recessive zebrafish mutant identified in an ENU mutagenesis screen. At 48 hpf, homozygous wil embryos display a small, dysmorphic heart with no clear distinction between ventricle and atrium, a pericardial edema and blood congestion at the inflow tract. To further assess wil heart morphology, we carried out whole-mount in situ hybridization with chamber-specific markers as well as immunofluorescence stainings using MF20/SF46 antibodys. Interestingly, wil mutant embryos express amhc and vmhc in both heart chambers. Furthermore, the atrium specific SF46 antibody stained both heart chambers, indicating a defective chamber specification on the molecular level. Using a classical positional cloning strategy, we identified a missense mutation in the spinster homolog 2 (spns2) gene as cause for the wil phenotype. SPNS2 is a known transporter of the signal molecule sphingosine-1-phosphate. Whereas high concentrations of a morpholino antisense nucleotide against spns2 caused cardia bifida (as has been shown in the zebrafish mutant two of hearts [1]), injection of low morpholino concentrations resulted in morphants displaying the wil phenotype, including the missing distinction between atrium and ventricle. Together with the fact that only approximately 10% of the descendants of heterozygous couples exhibited a wil heart phenotype and some homozygous mutant wil embryos displaying a wild type phenotype could be raised to adulthood, this suggests a hypomorphic character of the mutation. Rescue experiments were performed by injection of wild type spns2 mRNA into the one-cell stage of homozygous wil embryos, resulting in normal heart morphology and blood circulation. Stability and localization data indicated that neither a degradation nor a delocalization of the mutant SPNS2 protein is the reason for the wil phenotype, implying an insufficient S1P transport as cause. Taken together our results suggest that the mutation in wil embryos causes not a complete but a partial loss of SPNS2 function and interferes with chamber specification in the embryonic zebrafish heart.

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# Loss of Histone deacetylase 1 leads to cardiac hypoplasia in zebrafish

Junior Research Alliance SYMBOL-HF

**Presenting Author: Anja Bühler**

Anja Bühler, Sofia Hirth, Steffen Just

University Hospital of Ulm Internal Medicine II Molecular Cardiology Albert-Einstein Allee 23 89081 Ulm

Myocardial infarction in humans leads to cardiomyocyte (CM) death, followed by the formation of an irreversible, noncontractile fibrotic scar and eventually heart failure. This inability to regenerate the damaged tissue is mainly due to the postmitotic state of mammalian CMs. By contrast, the zebrafish is able to regenerate functional cardiac muscle after injury through a robust proliferative capacity in the adult fish. To investigate the mechanisms controlling CM proliferation and regeneration, we characterized the zebrafish mutant baldrian (bal), which we isolated in an ENU mutagenesis screen. Bal mutants display a pericardial edema, bradycardia and a thin walled myocardium. By positional cloning we identified a missense mutation in the Histone deacetylase 1 (HDAC1) gene. In confirmation experiments, we were able to phenocopy the bal phenotype by morpholino (MO) mediated knock-down of HDAC1. We counted CMs at 72 hpf and observed a significant decrease in CM number in bal mutant embryos compared to their wild type littermates. To investigate the amount and proper differentiation of cardiac precursors an in situ hybridization using probes against cardiac transcription factor nkx2.5 and cardiac myosin light chain 1 (cmlc1) was performed. Thereby a normal expression pattern of these two cardiac specific markers was found in bal embryos, suggesting a proper precursor number and commitment to the cardiac lineage. In order to determine, whether the decreased number of CMs is due to reduced proliferation or to an elevated apoptotic rate, EdU and TUNEL stainings were carried out. The TUNEL assay showed no alteration in the number of apoptotic CMs between the bal mutant and their wild type littermates. By EdU stain we revealed a reduced proliferation rate as cause for the hypoplastic phenotype of the bal mutants. In our ongoing research, we currently investigate the detailed molecular mechanism by which HDAC1 regulates proliferation and cell cycle progression in embryonic zebrafish CMs.

e:Med
SYSTEMS MEDICINE

# Poster Presentations
# IV Computational Approaches & Clinical Utilities

# Towards Clinical Systems Medicine: IT components for decision support

Consortium CLIOMMICS

**Presenting Author: Matthias Ganzinger**

Matthias Ganzinger, Matthias Gietzelt, Christian Karmen, and Petra Knaup

Heidelberg University, Institute of Medical Biometry and Informatics, Heidelberg, Germany

The e:Med initiative and others define Systems Medicine as the transfer of methods from Systems Biology to the level of patient treatment. Such approaches are valuable to gain a better understanding of diseases by models describing disease-specific mechanisms. Beyond that, Systems Medicine strives for an individualized prognosis and treatment of patients on the basis of heterogeneous data including omics data as well as phenotype data, patient lifetime environment or individual preferences. Complex diseases like cancers are especially suited to be addressed by Systems Medicine, thus, reference cohorts and individual patients have to be described in many dimensions. Therefore, Systems-Medicine-based patient care is only possible with the help of appropriate information technology (IT). Such IT systems leverage Systems Biology models by applying them on an individual patient's data. Integrated representation of disease related data is only the first step in the pipeline of an IT system for Systems Medicine. These data have to be made available for the clinical decision making process to bring benefits for individual patients. IT-based clinical decision support systems (DSS) can be used for this task, but so far they usually do not cover all available data types. In the e:Med project "Clinically-applicable, omics-based assessment of survival, side effects, and targets in multiple myeloma " (CLIOMMICS) we developed a generic IT architecture for Systems Medicine. As replaceable DSS component we investigate the application of case-based reasoning (CBR) on Multiple Myeloma data including phenotype and omics data. We prepared a phenotype case base and achieved first results on using gene expression data with CBR. Currently, we investigate specific similarity and weighting measures. As a next step, we will research how the results of the DSS can be visualized for clinical use.

# A Systematic Literature Review on Current Methods and Data Sources for Systems Medicine

Consortium CLIOMMICS

**Presenting Author: Matthias Ganzinger**

Matthias Ganzinger, Matthias Gietzelt, Martin Löpprich, Christian Karmen, Petra Knaup

Heidelberg University, Institute of Medical Biometry and Informatics, Heidelberg, Germany

Background Systems medicine is a new approach for the development and selection of treatment strategies for patients with complex diseases. It is often referred to as the application of systems biology methods to medical practice. The objectives of this systematic literature review were to capture current use of (1) modelling methods and (2) data sources in systems medicine related research projects. Providing an overview of modelling methods is useful for future projects to select well-proven methods. For data sources it is important to know which sources are currently used and which other sources provide the potential for research to improve systems medicine approaches. Methods We queried the MEDLINE and ScienceDirect databases for papers associated with the search term systems medicine and related terms. The query term consisted of the search term “system medicine AND model“ which was expanded by respective plural forms. Papers were screened and assessed in full text in a two-step process according to the PRISMA statement. Results The queries returned 698 articles of which 34 papers were finally included into the study. A multitude of modelling approaches such as machine learning and network analysis was identified and classified. The modelling methods most often applied belonged to the class of machine learning methods. The most frequently mentioned data sources are electronic medical records and public databases (17.9 % each). More than one third (35.7 %) of the reported data sources relate to the group of literature, population data, and personal medical history. Discussion Currently, many different modelling approaches are used in systems medicine. However, the number of data sources included into the models is limited. Most projects currently focus on prognosis. To further leverage the potential of systems medicine, focusing on treatment strategies for patients and considering a broader range of data will be necessary.

# sysINFLAME – Data, Rules and Tools: A comprehensive approach to create an operational Systems Medicine toolbox

Consortium sysINFLAME

**Presenting Author: Christian Bauer, Ulrich Sax**

Christian Bauer (1), Carolin Knecht (2), Heike Lehmann (3), Andre Franke (4), Michael Krawczak (2), Marc-Thorsten Hütt (5), Ulrich Sax (1)

(1) Department of Medical Informatics, University Medical Center Göttingen, Göttingen, Germany (2) Institute of Medical Informatics and Statistics, Christian-Albrechts-University, Kiel, Germany (3) Medical Faculty, Christian-Albrechts-University, Kiel, Germany (4) Institute of Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany (5) Jacobs University, Bremen, Germany

In the era of “Big Data”, the production, integration and storage of medical research data may be regarded as the sole domain of biomedical informatics. However, many examples from both small and large research consortia in the past have shown that the success of systems medicine research projects rests on three pillars: data quality, data accessibility and data usability, where the latter also includes the availability of tools to enable and control the filtering, browsing, annotation and visualization of the data. The sysINFLAME consortium addressed the above issues by including a dedicated subproject (CP10, Data Management System) to facilitate access to the consortium data and to promote their analysis, together with CP9 ( Analysis and Systems Biology Dialog). Already accomplished tasks of CP10 include the following which will be addressed more detailed in upcoming publications: (1) sysINFLAME data overview sheet, (2) sysINFLAME Use & Access policy, (3) i2b2/tranSMART demonstrators and show cases, (4) tranSMART enhancements according to consortium needs: (a) On-the-fly microbiome analysis with phenotype grouping, (b) Management/data curation functionality, including outlier detection. After gradually solving some crucial infrastructure issues the IT-backbone of sysINFLAME is up and running. This includes a dedicated network segment on dedicated virtual platforms, created by the Kiel medical faculty. Another major focus of CP10 has been the establishment of a real world-compatible use and access policy for sysINFLAME. Putting the consent of patients or study participants at the center, several common rules could be agreed and a data use and access committee was set up. We chose the open source software i2b2/tranSMART as our tool for filtering, browsing, and visualizing the consortium data drawing upon long term collaboration with Zak Kohane, head of the Biomedical Informatics Department at Harvard Medical School in Boston, MA, USA, Paul Avillach and Shawn Murphy. The PI of CP10 attended the annual i2b2 Academic User’s Group meeting in Boston in June 2015 and a CP9/10 team participates actively in the 3rd EU i2b2 meeting, this year in Leicester, UK. Following the above data-rules-tools approach, CP10 can offer sysINFLAME members and partners a multitude of data sources, thereby laying the foundation for the overarching goal of the e:Med projects – the link to systems medicine applications.

# Identifying high-risk neuroblastoma co-driver genes and pathways using module networks

Consortium SYSMED-NB

**Presenting Author: Dilafruz Juraeva**

Dilafruz Juraeva (1), Frank Westermann (2), Matthias Fischer (3), Benedikt Brors (1)

(1)Division of Applied Bioinformatics (G200), German Cancer Research Center, Heidelberg, Germany (2) Division of Neuroblastoma Genomics (B087), German Cancer Research Center, Heidelberg, Germany. (3) Children's Hospital, Department of Pediatric Oncology and Hematology, Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany

We tested the hypotheses that (i) perturbations in the neuroblastoma driver gene affect the expression of a group of genes that form a module, that (ii) perturbations influence the module genes expression through changes in the driver gene expression, that (iii) multiple regulators might be responsible for the change in the expression of both driver gene and module genes. We applied the algorithm CONEXIC to identify high-risk neuroblastoma modulator genes based on multi-omic profiles from over 200 tumors. Tumor gene expression profiles were generated using both transcriptome sequencing and microarray-based gene expression experiments. Change in gene copies were identified based on the data from whole-genome sequencing, microarray-based comparative genomic hybridization (aCGH), or microarray-based DNA methylation platforms. Single nucleotide variations were detected from the whole transcriptome sequencing data. Several genes which have been previously associated with neuroblastoma were identified as single modulators. This list included MYCN, DDX52, NTRK1, C21orf2, HLA-DQA1, and DEFB125. At a network level, we identified a module in which high MYCN and high BRD9 were required for upregulation of the module genes. Gene-set enrichment analysis showed that the MYCN & BRD9 regulated module was enriched with the genes involved in multi-drug resistance. The other joint modulators of MYCN were EFNB2, TP73, TNFRSF10D, NTRK1. In addition to MYCN, the gene NTRK1 might form a regulatory program with NME1, KIF1B, CAMTA1, PDGFA, TNFRSF25, DDX52 upregulating the genes involved in alternative promoter usage and N-linked glycosylation. Our findings might help to identify additional drug resistance mechanisms that could give insight into cotargeting strategies. The future work will focus on replicating the results using an independent data set.

# Agent-based tumour models to define adjuvant therapy approaches in gastric cancer

Consortium SYS-Stomach

**Presenting Author: Jaber Dehghany**

Jaber Dehghany, Azadeh Ghanbari, Michael Meyer-Hermann

Department of Systems Immunology, Helmholtz Centre for Infection Research, Braunschweig, Germany

Stomach cancer is a frequent form of cancer, where a limited progress has been made in its treatment. Under treatment conditions, in vitro, some responder cell lines of gastric cancer show modified motilities, while some other cell lines remain non-responder. Available therapies lead to a diversity of efficiencies, among the responder cell lines, to control the motility of cancer cells. Moreover, modified cell motilities under treatment conditions are measured in culture dishes and reflect single cell behaviour rather than collective behaviour of the cells. We develop an agent-based model to predict the impact of therapies targeting cell motility onto the organisation of cells inside tumours. This enables us to connect the in vitro data of cell motility to tumour morphology as well as metastasis probability. Moreover, effects of different cell properties (such as adhesion and cell persistence length), as system parameters, can be investigated in a given parameter range. With an agent-based model it is possible to exploit the therapeutic potential of relevant drugs and predict optimal doses / dose schedules. The known correlation of cancer cell motility with the probability of metastasis may open new strategies of cancer therapy.

# Analysis of the TRAIL-induced apoptosis and ERK-MAPK signal transduction pathways in melanoma cell lines by a probabilistic Boolean network approach

Demonstrator Melanoma sensitivity

**Presenting Author: Philippe Lucarelli**

Philippe Lucarelli1, Sébastien De Landtsheer1, Panuwat Trairatphisan1, Thomas Sauter1

1Systems Biology group, Life Sciences Research Unit, University of Luxembourg, Luxembourg

Despite remarkable scientific and clinical efforts in melanoma research, the incidence of malignant melanoma-related skin cancer strongly increased over the last few decades. While metastatic melanoma is often characterized by mutations of the kinase BRAF, the large number of different mutations represent the biggest challenge in our understanding of the disease. These mutations lead to a very aggressive form of cancer with a usually poor prognosis. The response to chemotherapies only lasts for a few months until drug resistance usually occurs, leading to a relapse of the cancer. The goal of this study is to identify the critical mechanisms leading to drug resistance in the different melanoma cell lines. For an in-depth signal transduction pathway analysis of melanoma resistance to chemotherapies, we apply a systems biology approach which integrates experimental data into a mathematical model to unravel complex mechanisms. A mathematical model based on the TRAIL-induced apoptotic and ERK-MAPK signal transduction pathways will be established and refined based on newly acquired experimental data. Here, we employ a probabilistic Boolean network (PBN) modeling approach which allows large-scale modeling of molecular interactions and regulations among signaling molecules with minimal parameterisation. This approach can be applied to identify the influence of targeted molecules via different signaling pathways to induce apoptosis. Furthermore, to identify mechanisms counteracting drug resistance in malignant melanoma, sensitivity analysis will be performed on the PBN models of BRAF-MEK and apoptotic signaling pathway to identify the most sensitive points in the network which allow to formulate new hypotheses that can then be tested experimentally.

# Pathway-based integration of time-series omics data using public database knowledge

MMML-Demonstrators

**Presenting Author: Astrid Wachter**

Astrid Wachter, Tim Beissbarth

Department of Medical Statistics, University Medical Center Göttingen, Germany

The increased generation of omics data on different functional levels of the cell represents a constantly growing challenge for their analysis and interpretation. Time-series measurements add another dimension of complexity but likewise enable deeper characterization of biological processes. We developed a straightforward systems biology approach for the integrative analysis of time-series data from different high-throughput technologies based on pathway and interaction models from public databases. Implemented in our software tool 'pwOmics' this approach performs pathway-based level-specific data comparison of coupled human proteomic and genomic/transcriptomic data sets. Separate downstream and upstream analyses are performed on the functional levels of pathways, transcription factors and genes/transcripts and integrated in the cross-platform consensus analysis. Via network reconstruction and inference methods (steiner tree, dynamic bayesian network inference) consensus graphical networks provide detailed insight into dynamic regulatory processes. With this approach we investigated a public data set comprising time-course mass-spectrometry and microarray data from EGF signaling in human mammary epithelial cells. Understanding the dynamics of the underlying physiological signaling mechanisms helps to characterize dysregulation processes in EGF signaling, which are observed in many human malignancies, e.g. cancer. Regulatory consensus profiles could be identified that help understanding complex pathway interdependencies and feedback mechanisms. Integration of coupled high-throughput time-series data enables a highly comprehensive interpretation of time-dependent signaling. Our approach exploits public database knowledge and cross-platform omics data in order to generate hypotheses on the succession of underlying pathway interplay mechanisms.

# Toward modeling transcription factor activity in cancer

Junior Research Alliance MILES

**Presenting Author: Michael Rauer**

Michael Rauer and Mathieu Clément-Ziza

CMMC, University of Cologne, Cologne, Germany

The e:Med junior reserach aliance MILES aim at understanding lineage-specific signaling dependencies in cancer. In this frame-work, we want to summarize the tumor complexity through the inference of transcription factor activity. Indeed, cells, tissues and organs obtain their specificities through the set of genes they express. This transcriptional program is executed by specific transcription factors (TF) that directly or indirectly bind DNA and control gene expression levels. TFs are thus highly relevant. The activity of a TF cannot be evaluated by looking at its mRNA expression level; TF activity is dependent on its activation via transitional post-translational modifications and its association with cofactors, which cannot be measured at high-throughput. We are integrating TF binding data with the expression profiles of tumors to infer TF activities. To establish the list of the TF – targets relationship (ie which genes are regulated by which TF), we use existing chromatin immunoprecipitation coupled with deep-seqencing (ChIP-seq) data, together with methods allowing to go from the Chip-seq picks to the target genes (Sikora-Wohlfeld et al., 2013). In each tumor, the gene expression levels can be expressed as a function of the activity of the TFs that regulate them by using generalized linear models. We are inferring TF activity from these models. Finally to assess the performance of our method, we are exploiting cell line expression data in which TF has been knock-down.

Reference

Sikora-Wohlfeld, Ackermann, Christodoulou, Singaravelu, and Beyer (2013). Assessing computational methods for transcription factor target gene identification based on ChIP-seq data. PLoS Comput. Biol. 9, e1003342.

# Stochastic spike train models capture temporal patterns in perceptual responses to a bistable stimulus

Junior Research Alliance PsychoSys

**Presenting Author: Stefan Albert**

Stefan Albert (1), Christian Kubitza (1), Katharina Schmack (2), Gaby Schneider (1)

(1) Institute of Mathematics, Goethe University Frankfurt (2) Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin

In the firing activity of dopaminergic (DA) neurons typical patterns show two properties: They are oscillatory with a more or less strong degree of regularity, and rhythmic firing can occur in clusters of events (bursts) or in individual events. To capture these properties, a stochastic model has been proposed (GLO, Gaussian Locking to a free Oscillator, [1]) that characterizes the regularity of the oscillation and the number of events per burst with four interpretable parameters. Here we study time series of responses to continuous or intermittent presentation of a bistable stimulus investigated in schizophrenia patients and healthy controls [2,3]. Interestingly, these time series show similar properties as DA spike trains, i.e., oscillatory behavior [4] with single percept changes during continuous presentation or stable periods followed by bursts of percept changes during intermittent presentation. In addition, we observe group differences in the change from continuous to intermittent presentation. In order to investigate these differences and to relate parameters on the neuronal and perceptual level, we fit the GLO and a hidden markov model to the time series of percept changes. This requires new methods using Bayesian estimation that can deal with small numbers of events. The observed differences between processes with clusters of percept changes and with single events can be represented in both models. In addition, an increase in regularity from continuous to intermittent presentation [4] is represented in increased locking of percept changes to the oscillation, while the regularity of the oscillation remains unchanged.

Acknowledgements
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# Poster Presentations
# V Cancer

# Automated targeted 3D imaging of tissue microarrays for telomere analysis in prostate cancer

Consortium CancerTelSys

**Presenting Author: Manuel Gunkel**

Manuel Gunkel(1) Stefan Wörz(2) Katharina Deeg(3) Roland Simon(4) Guido Sauter(4) Karl Rohr(2) Karsten Rippe(3) Holger Erfle(1)

1) ViroQuant-CellNetworks RNAi Screening Facility, BioQuant, Uni-Heidelberg 2) University of Heidelberg, BioQuant, IPMB, and DKFZ Heidelberg, Dept. Bioinformatics and Functional Genomics, Biomedical Computer Vision Group , 3) Research Group Genome Organization & Function, DKFZ and BioQuant 4) Department of Pathology, Universitätsklinikum Hamburg-Eppendorf (UKE)

The pathological analysis of microscopy images from tissue samples provides valuable diagnostic information. However, in many instances it relies on the manual inspection of 2D images with relative low resolution of a limited section of the sample. As the signal distribution is frequently heterogeneous, this approach is prone to yield results that reflect a biased selection of the information present in the image and ignores subcellular details. To address these issues, we introduced a novel automated confocal fluorescence microscopy screening approach termed 3D-TIM for 3D Targeted IMaging. In a proof-of-concept we apply 3D-TIM to characterize the telomere length distribution in prostate cancer samples on a tissue microarray. The results obtained are used to identify the telomere maintenance mechanism of a given patient sample. The 3D-TIM workflow consists of (i) scanning the whole tissue sample in 2D, (ii) analyzing images on-the-fly to identify regions of interest, e.g., nuclei showing telomere signal, (iii) feeding back the corresponding positions to the microscope, and (iv) acquiring high-resolution multicolor 3D images for an in-depth automated analysis of subcellular structures at these regions. In this manner imaging speed is increased and data volume is reduced so that a 3D analysis of representative cellular substructures becomes possible. From the resulting data, information on the disease state is obtained in a well-defined and reproducible manner. We anticipate that 3D-TIM will prove to be useful for a wide range of clinical applications that involve the analysis of tissue samples.

# Non-invasive characterization of tumor progression in advanced HCC mouse models using different genetic origins and corresponding response to Sorafenib treatment using combined PET/MRI

Consortium Multiscale HCC

**Presenting Author: Patricia Wenk**

P. Wenk1, F. Heinzmann2, L. Zender2, A. M. Schmid1, B. J. Pichler1

1 Werner Siemens Imaging Center, Department of Preclinical Imaging and Radiopharmacy, University Hospital Tuebingen, Tuebingen, Germany 2Division of Translational Gastrointestinal Oncology, Department of Internal Medicine I, University Hospital Tuebingen, Tuebingen, Germany

Hepatocellular carcinoma (HCC) constitutes the second most common cause of cancer related death worldwide, a fact that is largely attributed to the lack of effective treatment options. Nowadays the multikinase inhibitor Sorafenib is approved for treatment of advanced HCC prolongs the median survival only for 2.8 months. Moreover, the therapy-related tremendous side effects highlight the need to improve HCC therapy. Evaluation of treatment response related to genetic origin requires a highly physiological HCC mouse model. Progression of c-Myc/N-RasG12V driven tumors was characterized longitudinally over a three weeks treatment period using combined PET/MR imaging once weekly. Treatment efficacy was compared to a vehicle-treated control group (n=~4 per tracer/group). Dynamic and static PET measurements were performed addressing angiogenesis ([68Ga]NODAGA-RGD), glucose consumption ([18F]FDG) and proliferation ([18F]FLT), while T2-weighted MRI served as anatomical reference for a detailed volumetric analysis of tumor and liver growth. Additionally, progression of tumors with different oncogenic drivers (c-Myc-/Akt-1) was monitored longitudinally using [18F]FDG PET/MRI. At the end of the experiment, tissue samples were collected for ex-vivo analysis. Control as well as treated mice showed high glucose consumption in liver and tumor tissue. However, treatment with Sorafenib led to a remarkably higher perfusion peak and to reduced angiogenesis. Tumors, that were clearly identified by MRI showed characteristic [18F]FDG time activity curve. Ex-vivo analysis, e.g. autoradiography and histology, of both genotypes show remarkable differences between control and treatment group. We present first results of remarkable influence of Sorafenib treatment towards HCC progression confirmed by in-vivo and ex-vivo analysis, also investigating a detailed connection with the tumors' genetic origins.

# Systems Biology Supports Multiscale Analysis of Imaging, Omics and Clinical Data to Improve Diagnosis and Therapy of HCCs

Consortium Multiscale HCC

**Presenting Author: Michael Bitzer / Claudia Zwingmann**

Bitzer M1, Bezrukov I2, Dammeier S3, Daum V4, Hahn D4, Heinzmann F1, Horger M5, Joshi T6, Kang TW1, Kenar E7, Kohlbacher O7, la Fougère C8, Lapin A6, Nahnsen S7, Nikolaou K5, Perfahl H6, Reuss M6, Schmid A2, Sipos B9, Wenk P2, Zender L1, Zwingmann C2,Malek N1, Pichler B2

1Internal Medicine I, University Hospital Tuebingen, Tuebingen, Germany 2Werner Siemens Imaging Center, Department of Preclinical Imaging and Radiopharmacy, University Hospital Tuebingen, Tuebingen, Germany 3Medical Proteome Center, Institute for Ophthalmic Research, University of Tuebingen, Tuebingen, Germany 4Chimaera GmbH, Erlangen, Germany 5Diagnostic and Interventional Radiology, University Hospital Tuebingen, Tuebingen, Germany 6Stuttgart Research Center Systems Biology, University of Stuttgart, Stuttgart, Germany 7Applied Bioinformatics, University of Tuebingen, Tuebingen, Germany 8Nuclear Medicine, University Hospital Tuebingen, Tuebingen, Germany 9Pathology, University Hospital Tuebingen, Tuebingen, Germany

HCC is now the third leading cause of cancer deaths worldwide and rising in incidence. Our interdisciplinary consortium covers all required areas of clinical disciplines, advanced mouse models, multimodal imaging, image and omics analysis, data mining, modeling and bioinformatics. In first steps, we developed state of the art liver cancer mouse models to generate orthotopic HCC of defined genetic origin, which mirror tumor development of advanced HCC. In these models, the histological and oncogenomic profiles closely resembled human HCC. After thorough characterization of the tumor vasculature, these models, with tumors of different oncogenic drivers, were subjected to in vivo imaging techniques, adressing glucose metabolism, proliferation, angiogenesis and hypoxia, to investigate longitudinally tumor progression. Treatment with the multikinase inhibitor Sorafenib, which represents a clinically approved gold standard of care for HCC, led to a remarkable reduction in tumor growth and angiogenesis. Our existing base of multifunctional imaging data was translated to patients with HCC under treatment with Sorafenib or transarterial chemoembolisation (TACE), which discovered new clinical predictors of the vascular system and tumor cells. Multiparametric PET/MR with FDG, Cho and perfusion-MRI was shown to reveal separate tumors with different functional properties within the same patient. As an essential steps towards multimodal analysis, we collaboratively developed image coregistrations of animal and human data, data mining solutions, and implemented sample- and datamanagement workflows. Our innovations and data clearly showed previously unidentified potentials of anatomical and functional imaging and tracer combinations to follow up heterogenous tumor properties. The progression of these studies will help in clinical management of HCC in terms of early diagnosis and treatment response, enabling precise stratification of responders and non-responders before therapy.

# CYP3A5 mediates resistance to small molecule inhibitors in a subtype of pancreatic ductal adenocarcinoma

Consortium PANC-STRAT

**Presenting Author: Martin R. Sprick**

Elisa M. Noll1,2†, Christian Eisen1,2†, Elisa Espinet1,2, Albrecht Stenzinger3, Corinna Klein1, Vanessa Vogel1, Alexander Muckenhuber3, Christian Lutz4, Wiebke Nadler1, Matthias Schlesner11, Octavio Espinosa11, Christoph Springfeld10, Christoph Rösli1, Jan Engelhardt1,2, Franziska M. Zickgraf1,2, Peter Neuhaus5, Marcus Bahra5, Bruno V. Sinn6, Michael Kulke4, Xiaoqi Jiang7, Annette Kopp-Schneider7, Nathalia A. Giese8,9, Thilo Hackert8,9, Oliver Strobel8,9, Jens Werner8,9, Wilko Weichert3,9,10, Roland Eils11, Andreas Trumpp1,2,9† and Martin R. Sprick1,2,9†

1 Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM gGmbH), Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany 2 Divison of Stem Cells and Cancer, Deutsches Krebsforschungszentrum (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany 3 Department of Pathology, University of Heidelberg, Im Neuenheimer Feld 224, 69120 Heidelberg, Germany 4 Heidelberg Pharma GmbH, Schriesheimer Str. 101, 68526 Ladenburg, Germany 5 Department of General, Visceral and Transplantation Surgery, Charité-Universitätsmedizin Berlin, Augustenburgerplatz 1, 13353 Berlin, Germany 6 Institute of Pathology, Charité-Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, German 7 Division of Biostatistics, Deutsches Krebsforschungszentrum (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany 8 Department of General and Visceral Surgery, University Hospital Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany 9 German Cancer Consortium (DKTK), 69120 Heidelberg, Germany 10 National Center for Tumor Diseases (NCT), Im Neuenheimer Feld 460, 69120 Heidelberg, Germany 11 Division of Theoretical Bioinformatics, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany

† These authors contributed equally to this work.

Pancreatic ductal adenocarcinoma (PDAC) is clinically still treated as a single disease. We have generated patient-derived models representing the recently identified quasi-mesenchymal, classical and exocrine-like PDAC subtypes, and report a two-marker set facilitating patient stratification by immunohistochemistry. The subtypes show significant differences in overall survival and drug sensitivity, with the exocrine-like subtype being resistant to the tyrosine kinase inhibitors erlotinib and dasatinib, as well as the chemotherapeutic paclitaxel. Highly expressed cytochrome P450 3A5 (CYP3A5) actively metabolizes these compounds in the exocrine-like subtype, and pharmacological or shRNA-mediated CYP3A5 inhibition sensitizes tumor cells in vivo. Additionally, we investigated the transcriptional network underlying the subtype-specific CYP3A5 expression. Hence, these data show that exocrine-like PDAC adopts a highly effective detoxification mechanism akin to that of hepatocytes. Expression of CYP3A5 in other tumor entities suggests this pathway as an important target to overcome drug resistance and to predict response to therapy with small molecule drugs.

# PDAC and its stroma: heterogeneity from a two-compartment point of view

Consortium PANC-STRAT

**Presenting Author: Magdalena Büscher**

Elisa Espinet Hernández1,2, Christian Eisen1,2, Magdalena Büscher1,2, Silke Weisenburger1,2, , Elisa M. Noll1,2, Vanessa Vogel1, Corinna Klein1, Zuguang Gu3, Matthias Schelsner3, Chris Lawerenz3, Nathalia Giese5, Oliver Strobel5, Rienk Offringa5,8, Thilo Hackert5, Dirk Jäger9, Christoph Springfeld9, Roland Eils3,6,7, Wilko Weichert4, Martin R. Sprick1,2, † and Andreas Trumpp 1,2, †

1 HI-STEM - Heidelberg Institute for Stem Cell Technology and Experimental Medicine gGmbH, Heidelberg, Germany 2 Divison of Stem Cells and Cancer, DKFZ, Heidelberg, Germany 3 Division of Theoretical Bioinformatics, DKFZ, Heidelberg, Germany 4 Institute of Pathology, University Hospital Heidelberg 5 Department of General and Visceral Surgery, University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany 6 Heidelberg Center for Personalized Oncology (DKFZ-HIPO), Heidelberg 7 Department of Bioinformatics and Functional Genomics, Institute for Pharmacy and Molecular Biotechnology (IPMB) and BioQuant, Heidelberg University 8 Division of Molecular Oncology of Gastrointestinal Tumors, DKFZ Heidelberg 9 Medical Oncology, National Center for Tumor Diseases, Univerity Hopital Heidelberg † Equal contribution

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive disease with dismal prognosis. Despite extensive research and the discovery of several promising drug candidates, little progress in PDAC treatment has been reported in the last years. New technologies facilitating the molecular and genomic analysis of tumors have revealed the identification of subtypes for a number of tumor entities such as breast cancer or ovarian. The understanding of the genetic heterogeneity of PDAC has enormously increased in the last years. However, to date there are no established diagnostic, prognostic or predictive biomarkers for this disease. The progression of the disease is accompanied by an extensive desmoplastic reaction rendering PDAC as the solid tumor with highest stromal content (up to 90% of the total mass). In the frame of the PANC-STRAT we aim to study the stroma associated to PDAC and its heterogeneity between patients. To this end, we use two approaches: In one hand, we have developed a novel workflow to generate patient-derived orthotopic xenografts (PDX) and serum-free cell cultures from primary resected PDAC tumors. When re-injected into immunodeficient mice, these primary cells generate xenografts with high pathological similarity to the original patient tumor, including a prominent stromal presence. To explore the differences in the microenvironment associated to PDAC we have generated gene expression profiles for the stroma of a number of xenografts from our PDX models. Interestingly, the stroma associated to different subtypes of PDAC cells showed strong differences. Besides, we have performed RNA sequencing from different sub-populations isolated directly from fresh primary human PDAC tumors. By making use of a novel set of immunohistochemical markers we can identify the PDAC-subtype to which each patient belongs. Hence, the RNAseq data of the different tumor populations obtained from primary tumor material can be also easily studied in the context of PDAC-subtypes. We believe that these approaches will shed some light on how different stromal expression patterns are interconnected with different epithelial expression profiles and vice-versa. This information can be ultimately exploited for patient stratification and therapy.

# Modulation of the Keap1-Nrf2 Pathway – Targeting Protein-Protein/DNA Interactions

Consortium SMOOSE

**Presenting Author: Jörn Weisner**

Jörn Weisner, Stefano Tomassi, Bianca Wiedemann, Janina Niggenaber and Daniel Rauh

Technische Universität Dortmund, Department of Chemistry and Chemical Biology, Otto-Hahn-Straße 6, D-44227 Dortmund, Germany

The Keap1-Nrf2 pathway is crucial for the protection of cells against oxidative, electrophilic and xenobiotic stress and damage. Recent studies, however, revealed a “dark side” of Nrf2 implying detrimental and harmful influences upon dysregulation. Frequently occurring genetic lesions within Keap1 and Nrf2 as well as pathway hyperactivation have therefore been linked to increased resistance to chemo- and radiotherapy in a variety of solid tumors. Under basal conditions, the transcription factor Nrf2 interacts with the homodimerized substrate adaptor protein Keap1, triggering the ubiquitination and subsequent proteasomal degradation of Nrf2. In contrast, electrophiles and reactive chemicals such as cytotoxic anticancer drugs trigger the modification of cysteines of Keap1. The resulting conformational changes hamper the protein-protein interaction between Keap1 and Nrf2, thereby preventing Nrf2 from proteasomal degradation and inducing the expression of critical stress response and cytoprotective genes. Due to its ambiguous role in cell protection and tumor proliferation, modulators of this regulatory pathway are of particular interest especially with regard to cancer chemoprevention and improved cancer therapy. Here, we report on an innovative reverse chemical genetics approach aiming at the identification of selective Nrf2 inhibitors by targeting i) the Keap1-Nrf2 interaction and ii) the Nrf2-DNA complex. Therefore, we developed and established biochemical and biophysical assay systems allowing for high-throughput screening of compound libraries and enabling the detection of small molecule- and stapled peptide-based modulators of the Keap1-Nrf2 pathway. By combining structural biology with a structure-guided design, newly identified ligands will be characterized optimized and investigated in cellular systems.

# Design and synthesis of stapled peptides for the disruption of Nrf2-DNA-Interactions

Consortium SMOOSE

**Presenting Author: Bianca Wiedemann**

Bianca Wiedemann, Stefano Tomassi, Jörn Weisner, Jana Cvetreznik, Daniel Rauh.

Dortmund University, Faculty of Chemistry and Chemical Biology, Otto-Hahn-Straße 6, D-44227 Dortmund, Germany email: bianca.wiedemann@tu-dortmund.de

In recent years, a lot of effort has gone into the modulation of protein-protein-interactions (PPI) for targeting “non-druggable” proteins.1 Small molecules have shown some major drawbacks in this field, like a reduced number of interactions and low binding affinities. Here stapled peptides appear to have some advantages: They combine the ability to target large areas with the conformational restriction of macrocycles, thus proving to be less prone to degradation, showing an enhanced cell permeability, and less entropic penalty upon binding.2 A further step in this direction is the targeting of protein-DNA-interactions (PDI). The transcription factor Nuclear factor erythroid 2-related factor 2 (Nrf2) and its master regulator Kelch-like ECH-associated protein 1 (Keap1) are governors in the protection of cells against oxidative and xenobiotic stress.3 For nearly a decade, it has been known that this crucial interplay is abrogated in various human cancers.4 A mutation of either of the partners leads to disruption of the Nrf2-Keap1-interaction and thus renders Nrf2 constitutively active.5 Activated Nrf2 translocates to the nucleus and dimerizes with small Maf proteins for DNA binding and downstream activation of target genes.6 This antioxidative response contributes to drug resistance and enhanced cancer cell proliferation.7 Displacing Nrf2 at the DNA could render cancer cells more susceptible to chemotherapy and thus enhance its impact. A small library of hydrocarbon stapled peptides has been designed based on the DNA-binding sequence of Nrf2, considering the optimum position for the non-natural amino acids used for the introduction of the staple. The most promising derivative was further modified to enhance the binding affinity to the DNA.

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# The MCM complex is a critical node in the miR-183 signaling network of high-risk neuroblastoma cells

Consortium SYSMED-NB

**Presenting Author: Hedwig Deubzer**

Marco Lodrini (1), Victoria Schmidt (2), Gereon Poschmann (3), Kai Stühler (3), Olaf Witt (2), Angelika Eggert (1), Hedwig Deubzer (1)

(1) Charite - University Medicine Berlin, Department of Pediatric Hematology, Oncology and BMT, Berlin (2) German Cancer Research Center (DKFZ), Clinical Cooperation Unit Pediatric Oncology, Heidelberg (3) Heinrich-Heine University Düsseldorf, Molecular Proteomics Laboratory, Düsseldorf

Background: MYCN and HDAC2 jointly repress the transcription of tumor suppressive miR-183 in neuroblastoma. Enforced miR-183 expression induces cell death and inhibits anchorage-independent colony formation and xenograft growth in mice. Here, we aimed to unravel the miR-183 signaling network and analyze members of the MCM protein family as potential critical downstream targets. Methods: miR-183 regulated proteins were identified upon transient enforced expression by label free mass spectrometric analysis. Target validation was performed by transient transfection and HDAC inhibitor (HDACi) treatment of neuroblastoma cell models followed by western blot analysis. Results: Analysis of miR-183 or negative control transfected neuroblastoma cells identified 85 differential expressed proteins in a label free mass spectrometric approach. Six members of the minichromosome maintenance (MCM2-7) protein family were found to be lower expressed upon enforced miR-183 expression and subsequent annotation category enrichment analysis revealed a 14-fold enrichment in the protein module category “MCM”. MicroRNA target prediction software studies revealed that miR-183 is predicted to directly target several MCM proteins. Enforced miR-183 expression reduced endogenous MCM3, MCM5 and MCM7 protein expression in western blot, thus validating label free analysis. Treatment of neuroblastoma cell lines with pan-HDACi’s or selective inhibitors targeting HDAC2 resulted in decreased MCM protein levels. Conclusions: These data reveal MCM proteins as potential direct targets in the miR-183 regulated signaling network and critical nodes in the miR-183 mediated tumor suppressive phenotype in neuroblastoma.

# Identification of predictive response and resistance factors to targeted therapy in gastric cancer using a systems medicine approach

Consortium SYS-Stomach

**Presenting Author: Birgit Luber and Dieter Maier**

SYS-Stomach consortium: Birgit Luber (1), Simone Keller (1), Gwen Zwingenberger (1), Dieter Maier (2), Birgitta Geier (2), Fabian Theis (3), Jan Hasenauer (3), Sabine Hug (3), Michael Meyer-Hermann (4), Azadeh Ghanbari (4), Jaber Dehghany (4), Axel Walch (5), Alice Ly (5), Michaela Aichler (5), Florian Lordick (6), Ivonne Haffner (6)

(1) Institute of Pathology, Technische Universität München, München, Germany (2) Biomax Informatics AG, Planegg, Germany (3) Institute of Computational Biology, Helmholtz Centre Munich, Neuherberg, Germany (4) Department Systems Immunology, Helmholtz Centre for Infection Research, Braunschweig, Germany (5) Institute of Pathology, Research Unit Analytical Pathology, Helmholtz Centre Munich, Neuherberg, Germany (6) University Cancer Center Leipzig (UCCL), University Hospital Leipzig AöR, Leipzig, Germany

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer death worldwide. Mainly due to molecular and clinical heterogeneity, progress in the treatment of gastric cancer has been limited. The frequent overexpression of HER2 and EGFR in gastric cancer made these receptor tyrosine kinases particularly interesting for targeted therapies. However, the EGFR-targeted monoclonal antibodies cetuximab and panitumumab were not sufficiently effective in gastric cancer. One targeted agent that is approved in gastric cancer at present is the HER2-targeted monoclonal antibody trastuzumab. Unfortunately, an essential number of tumors are resistant to trastuzumab treatment; even initially responsive tumors can acquire resistance during the treatment. Therefore, specific markers are urgently needed to predict the efficacy of the therapy for the individual patient. We apply a knowledge and multi-data type integrating approach based on computational modelling of relevant aspects of the affected system, in this case signal transduction as well as phenotypic and/or molecular characteristics of gastric cancer cell lines and tumor samples. The SYS-Stomach consortium consists of experts across disciplines, including clinical partners, basic scientists and specialists for data management and mathematical modelling. The aim of the consortium is to identify response and resistance factors to targeted therapy with the HER2- and EGFR-directed antibodies trastuzumab and cetuximab in gastric carcinoma using a systems medicine approach and to identify specific differences of the cells in the reaction to both agents. These response and resistance factors are being developed by in vitro gastric cancer cell measurements and proteomic analyses of gastric cancer tumor samples in conjunction with mathematical modeling within the project and subsequently validated in patients samples which are being collected for instance within the multicentre study “VARIANZ”.

# Clinical validation of response and resistance factor candidates to targeted therapy in gastric cancer (GC)

Consortium SYS-Stomach

**Presenting Author: Ivonne Haffner**

Ivonne Haffner1 Birgit Luber2, Dieter Maier3, Birgitta Geier3, Fabian Theis4, Michael Meyer-Hermann5, Axel Walch6, Albrecht Kretzschmar7, Ludwig Fischer von Weikersthal8, Jorge Riera Knorrenschild9, Katrin Schierle10, Christian Wittekind10, Florian Lordick1

1University Cancer Center Leipzig (UCCL), University Hospital Leipzig, Leipzig, Germany 2Institute of Pathology, Technische Universität München, Munich, Germany 3Biomax Informatics AG, Planegg, Germany 4Institute of Computational Biology, Helmholtz Zentrum München Deutsches Forschungszentrum für Gesundheit und Umwelt, Munich, Germany 5Department of Systems Immunology and Braunschweig Integrated Centre of Systems Biology, Helmholtz Centre for Infection Research, Braunschweig, Germany 6Reserach Unit Analytical Pathology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany 7MVZ Mitte Leipzig, Germany 8MVZ Amberg, Germany 9Department of Hematology and Oncology, University Hospital Marburg, Germany 10Institute of Pathology, University Hospital Leipzig, Germany

Background: 10-20% of GC overexpress HER2, a membrane-bound receptor tyrosine kinase (RTK) which belongs to the epidermal growth factor receptor (EGFR) family. Drugs against HER2 and EGFR have shown variable success in the treatment of advanced GC. While EGFR targeting therapies failed to improve outcomes, trastuzumab addressing HER2 has been approved for stage IV HER2+ GC. Until now, primary and secondary resistance against RTK-directed treatment of GC is not well understood. The VARIANZ study, which is part of the SYS-Stomach consortium (supported by the German Federal Ministery of Education and Research, BMBF) aims to assess resistance mechanisms in HER2+ tumor samples from patients receiving trastuzumab. Methods: HER2 status was verified centrally by two pathologists (KS and CW). In a second step, samples will be used to validate resistance factors that are identified as interesting candidates by in-vitro and in-silico modelling within the consortium. Results: From 26 May 2014 to 31 July 2015, we have enrolled 142 patients in 30 active German sites in this ongoing project. At present, 105 samples were fully characterized for HER2 status by immunohistochemistry (IHC) and in-situ-hybridization (ISH). According to criteria from the Trastuzumab for Gastric Cancer (ToGA) study, 28 of 105 samples were HER2+ in central testing. In 16 samples that were diagnosed as HER2+ by local pathologists the HER2 status could not be verified centrally. 5 HER2- probes in local testing were characterized as HER2+ by central testing. Conclusions: HER2-expression in GC appeared to be heterogeneous and still not easy to assess. Variability between local and central HER2 assessment was significant. Robust biomarkers predicting resistance to HER2 and other target therapies are needed.

# De novo discovery of therapy-resistant gastric cancer tumour subpopulations using Matrix-Assisted Laser Desorption/Ionisation Mass Spectrometry Imaging

Consortium SYS-Stomach

**Presenting Author: Alice Ly**

SYS-Stomach consortium: Axel Walch (5), Alice Ly (5), Michaela Aichler (5), Birgit Luber (1), Simone Keller (1), Gwen Zwingenberger (1), Dieter Maier (2), Birgitta Geier (2), Fabian Theis (3), Jan Hasenauer (3), Sabine Hug (3), Michael Meyer-Hermann (4), Azadeh Ghanbari (4), Jaber Dehghany (4), Florian Lordick (6), Ivonne Haffner (6)

(1) Institute of Pathology, Technische Universität München, München, Germany (2) Biomax Informatics AG, Planegg, Germany (3) Institute of Computational Biology, Helmholtz Centre Munich, Neuherberg, Germany (4) Department Systems Immunology, Helmholtz Centre for Infection Research, Braunschweig, Germany (5) Institute of Pathology, Research Unit Analytical Pathology, Helmholtz Centre Munich, Neuherberg, Germany (6) University Cancer Center Leipzig (UCCL), University Hospital Leipzig AöR, Leipzig, Germany

Gastric cancer is the third leading cause of cancer death worldwide. Progress in the treatment of gastric cancer has been limited mainly due to molecular and clinical heterogeneity. The identification of markers that may indicate populations of treatment-responder or –resistant tumour cells is of particular interest. Matrix-Assisted Laser Desorption/Ionisation Mass Spectrometry Imaging (MALDI-MSI) is an emerging technology which combines microscopy with mass spectrometry, and enables the label-free imaging of different molecular classes, such as proteins, peptides, metabolites, lipids, and drugs in their native histological context. This is in comparison to liquid-based mass spectrometry in which spatial information is lost, or genomic and transcriptomic techniques which require selection of cell populations. MALDI-MSI has been successfully used to investigate proteomic heterogeneity in gastric cancer patients. Bioinformatic analysis of spectra from fresh-frozen gastric cancer tissue demonstrated molecularly distinct regions within different patient samples, representing phenotypic tumour subpopulations. The linking of these subpopulations to patients' clinical data revealed that a number of these subpopulations were associated with overall survival (P = 0.025). Measurements of small molecule metabolites (<1500Da) are increasing in importance as these levels reflect gene expression, protein function, metabolic pathways and environmental factors. Preliminary analysis of formalin-fixed paraffin embedded biopsies and whole-resected patient samples demonstrated by differences in endogenous metabolite distribution, indicating that metabolic heterogeneity occurs in gastric cancer. Taken together, we have increased the molecular characterization of gastric cancer and identified therapy resistant subclones using MALDI-MSI technology. These findings allow for greater insight into pathological processes in gastric cancer and the development of new targeted therapies.

# Role of ERBB receptors and its ligands in HER2-low breast cancer: Specific ERBB targeting to improve therapeutic strategies.

Demonstrator HER2Low

**Presenting Author: Mireia Berdiel**

Berdiel,M.1; Reinz,E.1; Breunig,C.1; Bott, A.1; Mitra,D.1; Sofyali,E.1; Burmester,S.1; Will,R.2; Hasmann, M.3; Korf, U.1; Wiemann, S.1

1 Division Molecular Genome Analysis, DKFZ, Heidelberg 2 Genomics and Proteomics Core Facility, DKFZ, Heidelberg 3 Roche Diagnostics, Penzberg

About 70-80% of primary breast tumors show low or no detectable expression of HER2 receptor. However, other members of the ERBB family of receptors tyrosine kinases (RTK) such as EGFR, ERBB3 and ERBB4, are frequently potent drivers of tumor progression, resistance and metastasis. Although treatment of patients expressing high levels of HER2 is well established, an elevated percentage of patients develop resistance to anti-HER2 targeted therapies. On the other hand, current treatment options for tumors expressing HER2 at low to moderate levels have been proven unsuccessful, claiming for new therapeutic strategies. Signaling via receptors of the ERBB family is wired within a complex network of cellular back-up routes that can maintain downstream signaling pathways. Even the inhibition of a single receptor commonly leads to the activation of other receptors maintaining signaling and phenotypes. Drug impact on signaling networks needs to be understood in the context of activating ligands derived by autocrine or paracrine mechanisms and by the tumor microenvironment. The e:Med HER2Low project aims to identify the tumorogenic role of the different ERBB members and its ligands in a panel of cell lines under the HER2 low/moderate background and also to define alternative therapeutic strategies in resistant cell line models. Cancer cell lines (e.g., T47D, MDA-MB-231, MCF7) were selected according to their HER2 low/moderate expression (Neve RM. Cancer cell, 2006) and were molecularly characterized by means of RT-PCR and western blot analysis. Whereas T47D and MCF7 showed elevated expression of ERBB3 and ERBB4, in MDA-MB-231 only EGFR was expressed at high levels. Treatment with anti-HER2 therapies in these cell lines did not induce changes in viability, confirming their independence of HER2 receptors. To study the role of ERBB receptors on resistance mechanisms, trastuzumab-resistant BT474 cell line (BT474 TrasR ) and tamoxifen-resistant MCF7 cell (MCF7 TamR ) were also included. While expression of ERBB3 and ERBB4 receptors in tamoxifen-resistant MCF7 (MCF7 TamR ) was increased compared with parental MCF7, in BT474 Trast R these receptors were mostly decreased. Because NRG1 is the preferred ligand for ERBB3 its impact on cancer cells was further explored. Stimulation of T47D and MCF7 with NRG1 increased its proliferation and induced phosphorylation of the PI3K-AKt pathway. Not effects were observed for MDA-MB-231. Expression of NRG1 in epithelial cancer cells showed to be very low and inversely correlated with ERBB3 and ERBB4 expression, suggesting the microenvironment as a main source for this ligand. An Isogenic TNBC cell line (MDA-MB-231) with inducible expression of ERBB3 will be used to further explore this signaling. The ERBB3/ERBB4-NRG1 axis appears to be highly relevant both for tumor progression and drug resistance. Its specific blockade using targeted therapeutic antibodies might be a promising strategy for treatment of HER2-low subtypes of breast cancer.

# Personalization of breast cancer treatment by protein activation profiling of Her2-low breast cancer

Demonstrator HER2Low

**Presenting Author: Eileen Reinz**

Eileen Reinz (1), Mireia Berdiel (1), Daniel Kaschek (4), Max Hasmann (2), Stefan Wiemann (1), Tim Beisbarth (3), Jens Timmer (4), Ulrike Korf (1)

(1) German Cancer Research Center, Heidelberg, Germany; (2) Roche Diagnostics GmbH, Penzberg, Germany ; (3) University of Göttingen, Göttingen, Germany; (4) University of Freiburg, Freiburg, Germany

Breast cancer is the most common cancer in women worldwide and a highly heterogeneous disease. The high degree of diversity between and within tumors as well as among cancer-bearing individuals, and the unknown mechanism of therapeutic resistance complicate cancer therapy. Only 20-30% of the primary tumors show an overexpression of the HER2 receptor and could be targeted well by chemotherapeutic agents including trastuzumab and pertuzumab. To address the larger number of breast cancer patients with tumors expressing low or moderate levels of HER2 along with other EGFR/ERBB receptors novel treatment strategies have to be found. Targeting EGFR or ERBB3 receptors with powerful drugs could be one approach to increase the survival of these patients. The overall aim of the HER2low Research Consortium is to pave the way for a personalized treatment of HER2low breast cancer:

- investigate the proteomic profile of the EGFR/ERBB signaling network in tumor samples as well in drug resistant cell lines
- identification of biomarkers for treatment prediction

Clinically relevant activation patterns will be analyzed quantitatively by reverse phase protein microarrays using a collection of more than 100 highly specific antibodies recognizing cancer-related signaling proteins, and other proteins. Additionally perturbation experiments will be done in cell lines expressing low levels of HER2, and ligand and receptor levels will be analyzed by quantitative immunoblot analyses or ELISA. In order to study the behavior of the receptors after drug treatment and ligand stimulation, a novel technical approach of image analysis allowing spatio-temporal investigation of ERBB receptor signaling will be employed. This approach is based on the quantitative analysis of 3D pictures obtained by confocal microscopy that will be analyzed by bioinformatic tools to establish a mathematical model for treatment prediction of HER2low breast cancers.

# Clinical application of a systems model of apoptosis execution as a prognostic tool in stage 3 colorectal cancer

Demonstrator Melanoma sensitivity

**Presenting Author: Markus Rehm**

Markus Rehm1,2, Manuela Salvucci1,2, Mattia Cremona1,3, Maximilian Wuerstle1,2, Clare Morgan1,3, Sarah Curry1,4, Robert O'Byrne1,2, Orna Bacon1,5, Sonali Dasgupta6, Nadege Rice7, Camilla Pilati7, Andreas U. Lindner1,2, Elisabeth Zink1,2, Lisa M. Schöller1,2, Lorna Flanagan1,2, Sinead Toomey3, Daniel B. Longley6, Mark Lawler6, Patrick G. Johnston6, Richard H. Wilson6, Manuel Salto-Tellez6, Sophie Camilleri-Broët7, Elaine W. Kay1,4, Deborah A. McNamara5, Bryan T. Hennessy1,3, Pierre Laurent-Puig8, Sandra van Schaeybroeck6, and Jochen H.M. Prehn1,2

1Centre for Systems Medicine, 2Department of Physiology & Medical Physics, 3Department of Molecular Medicine, Royal College of Surgeons in Ireland, Dublin 2, Ireland;

4Department of Pathology, 5Department of Surgery, Beaumont Hospital, Dublin 9, Ireland;

6Centre for Cancer Research and Cell Biology, School of Medicine, Dentistry and Biomedical Science, Queen's University Belfast, Belfast, United Kingdom;

7Faculté de Médecine, 8 UMR-S775 INSERM Laboratory, Université Paris Descartes, Paris, France

Following removal of the primary tumour, stage 3 colorectal cancer (CRC) is routinely treated by adjuvant 5FU-based genotoxic chemotherapy. The competency of tumour cells to execute apoptosis is considered to be essential for chemotherapy to be effective. Apoptosis execution is controlled by a complex and non-linear signalling interplay between the key regulators Apaf-1, Procaspase-9, Procaspase-3, Smac and XIAP. Here, we therefore investigated if mathematical systems modelling based on apoptosis protein quantities, protein interactions and turnover can serve as a tool to prognosticate CRC patient outcome. We quantified the nM expression amounts of apoptosis execution proteins in tumour lysates from 128 chemotherapy-treated stage III colorectal cancer (CRC) patients using reverse phase protein arrays and mathematically simulated apoptosis execution signalling in individual patient CRC tumours. This allowed us to calculate the competency of individual tumours to undergo apoptosis execution in response to 5FU-based chemotherapy. We found that the competency to execute apoptosis was significantly associated with recurrence free survival ($p < 0.05$). Our results demonstrate that our mathematical model of apoptosis execution can serve as a combinatorial systems biomarker that adds value to current prognostic clinicopathological features, such as TNM staging and lymphovascular invasion.
This research is supported by the European Union FP7 programme (FP7 APO-DECIDE).

# TIL-REP Junior Consortium - dynamics of the tumor infiltrating lymphocyte repertoire in melanoma and pancreatic cancer

Junior Research Alliance TIL-REP

**Presenting Author: Isabel Poschke**

Mustafa Diken, Michael Floßdorf, Isabel Poschke, Jessica Hassel, Oliver Strobel

TRON - Translationale Onkologie an der Universitätsmedizin der Johannes Gutenberg-Universität Mainz gGmbH; Deutsches Krebsforschungszentrum (DKFZ), Theoretische Systembiologie; Deutsches Krebsforschungszentrum (DKFZ), Molekulare Grundlagen Gastrointestinaler Tumore; Universitätsklinikum Heidelberg, Hautklinik und Nationales Centrum für Tumorerkrankungen; Universitätsklinikum Heidelberg, Klinik für Allgemeine, Viszerale und Transplantationschirurgie

Detection of tumor infiltrating lymphocytes (TIL) in human cancers and their positive prognostic impact indicate that the immune system is able to respond to tumors. Furthermore, harnessing the anti-tumor T-lymphocyte response by treatment with antibodies blocking negative regulatory signals (e.g. ipilimumab) or by in vitro expansion and reinfusion of TIL, can result in striking tumor reduction in patients with metastatic cancer.1-3 Based on previous experimental, clinical and computational work by its partners, the TIL-REP consortium is investigating the composition and dynamics of the TIL repertoire and its clinical implementations. We are pursuing these complementary approaches:

- Analysis of the TIL repertoire in human tumor biopsies by phenotypic characterization and T-cell receptor (TCR) sequencing
- Examination of the clonal dynamics of the TIL response in a well-defined mouse tumor model
- Establishment of a data-driven mathematical model to quantify and thus better understand the fundamental processes governing development of the TIL repertoire and simulate its response to immunotherapy

TIL-REP was inspired by our recent next-generation TCR-sequencing data, demonstrating that the TIL repertoire, compared to blood-derived T-cells, is enriched for certain TCRs that most likely represent tumor-reactive clones. Thus, TCR profiling is an exciting tool for charting the TIL response and can serve as a powerful biomarker, guiding development and evaluation of cancer immunotherapy. TIL-REP focuses on two cancer entities: melanoma and pancreatic ductal adenocarcinoma (PDA). While melanoma already offers a wealth of information on TIL responses, our recent PDA data indicate that T-cell-immunotherapy could offer promising new treatment options for this deadly disease.


# Poster Presentations
# VI Neurological Disorders

# Perceived Stress and Hair Cortisol: Differences in Bipolar Disorder and Schizophrenia

Consortium IntegraMent

**Presenting Author: Fabian Streit**

Fabian Streit1, Amra Memic2, Lejla Hasandedi 2,3, Liz Rietschel4, Josef Frank1, Maren Lang1, Stephanie H Witt1, Andreas Forstner5, Franziska Degenhardt5, Markus M. Nöthen5,6, Clemens Kirschbaum7, Jana Strohmaier1, Lilijana Oruc2*, Marcella Rietschel1*

1 Department of Genetic Epidemiology in Psychiatry, Medical Faculty Mannheim, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany 2Psychiatric Clinic, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina 3Psychology Department, Faculty of Letters, Akdeniz University, Antalya, Turkey 4University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern 5Institute of Human Genetics, University of Bonn, Bonn, Germany. 6Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany. 7Department of Psychology, Technische Universität Dresden, Dresden, Germany

Introduction Bipolar disorder (BD) and schizophrenia (SCZ) are psychiatric disorders with both shared and distinct clinical and genetic features. In both disorders, stress increases the risk for onset or relapse and dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis has been reported. The analysis of hair cortisol concentration (HCC) allows retrospective assessment of cortisol secretion (i.e. the previous three month) Aims To explore whether HPA regulation and perceived stress: (i) differ between an BD or SCZ patients and controls ii) differ between BD and SCZ; and (iii) change over BD or SCZ disease course. In addition, analyses were performed to determine whether an increased genetic risk for BD or SCZ in controls is associated with HCC or perceived stress. Methods 149 SCZ patients, 60 BD patients and 82 controls were included in the study. Controls and outpatients and were assessed at one time point, patients with an acute episode (77 SCZ and 38 BD) were assessed shortly after admission and at 3 and 6 months. Assessment included perceived stress, Hair cortisol concentrations and psychopathology. Polygenic risk scores for BD and SCZ were calculated based on results of the Psychiatric Genomic Consortium. Results Perceived stress was higher in BD and SCZ patients compared to controls. No difference was observed between BD and SCZ patients. In BD and SCZ inpatients, perceived stress decreased over the 6 month study period, and was lower in outpatients compared to inpatients at admission. HCC was higher in BD patients compared to SCZ patients and controls. Outpatients showed lower HCC than inpatients. The highest HCC s measures were observed i n BD inpatients, and these showed no significant decline over the 6 month study period. Correlation between perceived stress and HCC No correlation was found between perceived stress and HCC. Correlation of percieved stress and HCC with genetic risk BD and SCZ patients had higher genetic risk scores for BD and SCZ, respectively. In controls, the genetic risk score for BD, but not for SCZ, was associated with HCC. Conclusions While our results are consistent with previous reports of increased perceived stress in BD and SCZ, they suggest differential involvement of the HPA axis in the two disorders. The genetic study suggests that this effect is present below the threshold of manifest disorder.

# Validity of a self-rating questionnaire for major depressive disorder: Comparison with clinical interview data

Consortium IntegraMent

**Presenting Author: Jana Strohmaier**

Jessica Martin, Fabian Streit, Jens Treutlein, Maren Lang, Josef Frank, Andreas Forstner, Franziska Degenhardt, Stephanie H. Witt, Thomas G. Schulze, Sven Cichon, Markus M. Nöthen, Marcella Rietschel, Jana Strohmaier

Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany; Institute of Human Genetics, University of Bonn, Germany; Department of Genomics, Life & Brain Center, University of Bonn, Germany; Section on Psychiatric Genetics, Department of Psychiatry and Psychotherapy, University Medical Center, Georg-August-University Göttingen, Germany; Division of Medical Genetics, Department of Biomedicine, University of Basel, Switzerland; Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany.

Introduction: Recent years have witnessed the success of genome-wide association studies (GWAS) to the identification of genetic risk variants for psychiatric disorders. A limiting factor in terms of their further success is the lack of sufficiently large samples, particularly for disorders with modest heritability such as major depression (MD). While clinical interviews are the gold standard for diagnostic assessment, they are costly in terms of time and money, and self-rating questionnaires may represent a more efficient form of assessment in the GWAS context. The aim of the present study was to investigate the validity of self-rating questionnaires for MD by comparing the use of a self-rating questionnaire with clinical interview data. Methods: A sample of 475 population-based subjects from Germany was evaluated (249 men, 226 women; mean age=47.6 years, SD=14.9). Life-time clinical diagnosis and symptom severity of MD were assessed using the Structured Clinical Interview for DSM-IV Disorders Axis I (SCID-I) and a self-rating questionnaire which was adapted from the Inventory to Diagnose Depression (IDD). The following analyses were performed: (1) correlation between interview and questionnaire assessments of clinical diagnosis and symptom severity; (2) sensitivity and specificity of the questionnaire assuming that the interview elicited the “correct” diagnosis; and (3) odds of having a positive family history of MD (FH-MD+) if diagnosed with life-time MD by the questionnaire. Results: In the interview, 14.3% (men 8.1%, women 21.3%) were diagnosed with MD compared to 11.2% (men 7.5%, women 15.3%) using the questionnaire. Interview and questionnaire results were strongly correlated for clinical diagnosis ($r=0.624$, $p < 0.001$); and very strongly for symptom severity ($r=0.819$, $p < 0.001$). The concordance rate of questionnaire and clinical interview was 88%, i. e. 88% of individuals were assigned either a diagnosis of MD, or no MD diagnosis, by both assessment methods. Sensitivity of the questionnaire was 0.462 and its specificity was 0.948. Sensitivity was highest for the DSM-IV A criterion and consecutively decreased for the B, C, and D criterion (0.935, 0.838, 0.662, 0.455). 43% of individuals diagnosed with MD by the questionnaire had a FH-MD+ as

compared to 15% of individuals with no MD diagnosis (OR=4.28; $p < 0.001$). Conclusions: The prevalence of life-time MD identified using the interview corresponds to the 14% average prevalence reported in high-income countries. The questionnaire appeared to slightly underestimate this prevalence. The correlation between the diagnostic assessment of MD was higher for a continuous (symptom severity) than for a categorical phenotype (clinical diagnosis). The strong correlation coefficient for the continuous phenotype and the high sensitivity for the DSM-IV A criterion suggest that questionnaires can replace the interview in terms of symptom (severity) assessment. The high specificity suggests that individuals with no MD diagnosis can be identified reliably with the questionnaire. The high odds of having a FH-MD+, i. e. a higher genetic vulnerability, if diagnosed with MD by the questionnaire, underpins the validity of the questionnaire diagnosis. However, due to the low sensitivity of DSM-IV C and D criteria, the questionnaire is not able to identify individuals with life-time MD reliably. Thus in terms of a diagnosis of MD, our findings indicate that caution is warranted when considering the use of a self-report questionnaire in the GWAS context.

# Ethical considerations in predictive genetic testing

Consortium IntegraMent

**Presenting Author: Stephanie Witt**

Stephanie H Witt1, Jana Strohmaier1, Christine Schmäl1, Bert Heinrichs2, Maria Alex2, Dirk Lanzerath2, Marcella Rietschel1

1Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany; 2German Reference Center for Ethics in the Life Sciences, Bonn

Growing attention is given to clinical genetic testing and the questions raised about the value of such testing in psychiatry. The Imagemend consortium will combine neuroimaging, genetic, environmental and clinical data of patients with schizophrenia, bipolar disorder, attention-deficit hyperactivity disorder and controls to develop commercially viable, clinical tests for accurate patient stratification, prediction and treatment selection contributing directly to better patient outcomes. However, predictive clinical genetic testing also raises ethical questions which need to be addressed.To assess attitudes towards and understanding of diagnostic/predictive testing, evaluate which group of persons could benefit most from application of diagnostic and predictive testing, and address the concerns associated with the development and application of novel predictive genetic testing for mental illness, we have developed a questionnaire on attitudes of predictive genetic testing. As a basis for a Delphi process, we have assessed the attitudes and ethical views of patients, relatives, health care professionals, and the general population towards such genetic predictive testing, as well as their precise understanding of the results and the perceived benefit of such risk predictions. Results show a diversity in attitudes on predictive genetic testing and a necessity for further education on this topic. Also, within the context of genetic counselling, predictive risks are often difficult for individuals to understand. Results of the questionnaire will be used to prepare a Delphi process. The delphi process will involve experts (psychiatrist, patient, relative, lawyer, lay person) which will discuss the usefulness of previously developed case-vignettes, i.e. scenarios of persons for whom testing will be feasible, in delphi rounds. Results will be used for interviews with potential consumers, i. e. patients, relatives, persons at risk and providers i. e. health care professionals to assess attitudes, expectations, fears, understanding of information, and the conclusions drawn with respect to diagnostic and predictive genetic testing.

# Neuropeptide Y Receptor Y2 (NPY2R) Promotor Variant rs6857715 in Major Depression and Major Depression-Associated Appetite Increase and/or Weight Gain

Consortia IntegraMent / SysMedAlcoholism

**Presenting Author: Jens Treutlein**

Jens Treutlein,1* Jana Strohmaier,1* Josef Frank,1 Stephanie H. Witt,1 Andreas J. Forstner,2,3 Maren Lang,1 Franziska Degenhardt,2,3 Helene Dukal,1 Stefan Herms,2,3,4 Fabian Streit,1 Per Hoffmann,2,3,4 Christine Schmäl,1 Sven Cichon,2,3,4 Markus M. Nöthen,2,3 Marcella Rietschel1#
*shared primary authorship, #corresponding author

1Dept. of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Germany; 2Institute of Human Genetics, University of Bonn, Germany; 3Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany; 4Division of Medical Genetics and Department of Biomedicine, University of Basel, Switzerland

Stress increases the risk for depression, alcohol abuse, and over-eating, and is modulated by the NPY system. The T-allele of rs6857715 at the NPY2R locus, which was described as non-pathogenic in higher primates, has been associated with obesity in humans (Zhang et al. 2010, Hum Mutat 31:1286-1293). The C-allele has been associated with alcohol dependence. We examined the possible association with major depression in 595 patients and 1295 controls, and in 84 patients suffering of increased appetite and/or weight gain as a core symptom of their depression. Major depression was associated with the C-allele (P=0.020 [two-sided]). The T-allele, however, was more frequent in patients displaying increased appetite and/or weight gain, compared to those who did not (P=0.054 [one-sided]). This underlines the importance of examination of more refined phenotypes than solely categorical diagnoses. Replication and investigation in stress-related disorders may generate insights into biological mechanisms acting across somatic and psychiatric diagnoses.

# Genome-Wide Association Study of Pathological Gambling

Consortium SysMedAlcoholism

**Presenting Author: Maren Lang**

Maren Lang, PhD1; Tagrid Leménager, PhD2; Fabian Streit, MSc1; Mira Fauth-Bühler, PhD2; Josef Frank, MSc1; Dilafruz Juraeva, PhD3; Stephanie H. Witt, PhD1; Franziska Degenhardt, MD4; Andrea Hofmann, PhD4; Stefanie Heilmann-Heimbach, PhD4; Falk Kiefer, MD, Prof.2; Benedikt Brors, PhD, Prof. 3; Hans-Jörgen Grabe, MD, Prof.5; Ulrich John, PhD, Prof. 6,9; Anja Bischof, PhD 7; Gallus Bischof, PhD 7; Uwe Völker, PhD, Prof.8,11; Georg Homuth, PhD8; Monika Vogelsang, MD12; Martin Beutel, MD,13; Henry Völzke, MD, Prof.9,11; Markus M. Nöthen, MD, Prof. 4; Christian Meyer, PhD, Prof. 6,9; Hans-Jürgen Rumpf, PhD7; Friedrich M. Wurst, MD, Prof. 10; Marcella Rietschel, MD, Prof1.; Karl F. Mann, MD, Prof.2

1Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim/ Heidelberg University, Mannheim, Germany. 2Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, Medical Faculty Mannheim/ Heidelberg University, Mannheim, Germany. 3Division of Applied Bioinformatics, German Cancer Research Center, Heidelberg, Germany. 4Institute of Human Genetics, University of Bonn, Bonn, Germany; Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany. 5Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Helios Hospital Stralsund, Germany; German Center for Neurodegenerative Diseases (DZNE), Rostock/ Greifswald, Germany. 6Department of Social Medicine and Prevention, University Medicine Greifswald, Greifswald, Germany 7Department of Psychiatry and Psychotherapy, University of Luebeck, Luebeck, Germany. 8Department of Functional Genomics, University Medicine Greifswald, Greifswald, Germany. 9Institute for Community Medicine, University of Greifswald; Greifswald, Center for Dental, Oral and Maxillofacial Medicine, University of Greifswald, Institute of Social Medicine and Prevention, University of Greifswald, Germany. 10Christian-Doppler-Klinik, Salzburg, Austria 11Partner site Greifswald, (DZHK) German Centre for Cardiovascular Research, Greifswald, Germany. 12Clinic for psychosomatic medicine, psychotherapy, and addiction medicine, AHG Klinik Münchwies, Neunkirchen, Germany 13Kraichtal-Kliniken, Kraichtal, Germany

Background: Pathological gambling is a behavioural addiction with negative economic, social, and psychological consequences. Identification of contributing genes and pathways may improve understanding of aetiology and facilitate therapy and prevention. Here, we report the first genome-wide association study in pathological gambling. Our aims were to identify pathways involved in pathological gambling and examine whether there is a genetic overlap between pathological gambling and alcohol dependence. Methods: 445 individuals with a diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders of pathological gambling were recruited in Germany, and 986 controls were obtained from a German general population sample. A genome-wide association study of pathological gambling comprising single marker-, gene-based-, and pathway-analyses was performed. Polygenic risk scores were generated using data from a German genome-wide association study of alcohol dependence. Results: No genome-wide significant association with pathological gambling was found for single markers or genes. Pathways for Huntington's

disease (p-value = 6.63 x 10-3), the 5’ adenosine monophosphate-activated protein kinase signalling pathway (p-value = 9.57 x 10-3), and apoptosis (p-value = 1.75 x 10-2) were significant. Polygenic risk score analysis of the alcohol dependence dataset yielded a one-sided nominal significant p-value in subjects with pathological gambling, irrespective of co-morbid alcohol dependence status. Discussion: The most significant pathway analysis finding suggests shared pathology between Huntington’s disease and pathological gambling. This is consistent with previous imaging studies. The present results also accord with quantitative formal genetic studies which had shown genetic overlap between non-substance- and substance-related addictions.


# Poster Presentations
# VII Infection and Inflammation

# CAPSyS – Systems Medicine of Community Acquired Pneumonia – A consortium investigating the course of pneumonia from infection to resolution

Consortium CAPSyS

**Presenting Author: Peter Ahnert**

P. Ahnert(1), M. Scholz(1), N. Suttorp(2), P. Creutz(2), J. Vera-Gonzalez(3), B.Schmeck(4), M. Witzenrath(2), M. Kiehntopf(5), M. Bauer(6), T. Chakraborty(7), H.M. Hossain(7), U. Völker(8), H. Binder(9), M. Löffler(1,9)

(1)Universität Leipzig, Institute for Medical Informatics, Statistics, and Epidemiology (IMISE), Leipzig, Germany (2) Charité - Universitätsmedizin Berlin, Department of Infectious Diseases and Respiratory Medicine, Berlin, Germany (3) Universitäts-klinikum Erlangen, Hautklinik, Arbeitsgruppe Systems Tumor Immunology, Erlangen, Germany (4) Philipps Universität Marburg, Institut für Lungenforschung, Marburg, Germany (5) Friedrich Schiller Universität Jena, Mediz. Fakultät, Institut für Klinische Chemie und Laboratoriumsdiagnostik, Jena, Germany (6) Friedrich Schiller Universität Jena, Universitätsklinikum, Klinik für Anästhesiologie und Intensivmedizin, Jena, Germany (7)Justus-Liebig-Universität Gießen, Medizinische Mikrobiologie, Gießen, Germany (8) Universitätsmedizin Greifswald KöR der Ernst Moritz Arndt Universität Greifswald, Funktionelle Genomforschung, Greifswald, Germany (9) Universität Leipzig, Medizinische Fakultät, Interdisziplinäres Zentrum für Bioinformatik, Leipzig, Germany

CAPSyS is a consortium of the e:Med initiative investigating the course of pneumonia from infection to resolution. CAPSyS uses a systems medicine approach to identify new molecular and clinical signatures predicting imminent lung barrier failure in patients with hospitalized, community acquired pneumonia (CAP) and to generate new insights into relevant pathomechanisms. Research is organized in five sub projects at seven locations, with support by external partners: TP 1 - Integrative Genetic Analysis and Biomathematical Modelling of Systemic Inflammation (Leipzig) TP 2 - Deep phenotyping in patients with severe CAP and new analyses in established cohorts (Berlin, Jena, Gießen, Greifswald) TP 3 - Mathematical modelling of pneumonia pathophysiology (Erlangen) TP 4 - Experimental modelling and validation of pneumonia pathophysiology (Marburg, Berlin, Jena, Gießen, Greifswald) TP 5 - Platform for Data-Integration, Communication, Data Mining, and Project Management (Leipzig) CAPSyS focuses on severe disease course, involving loss of barrier function in alveoli and leading to spread of infection beyond the lung (sepsis). An initially localized response of the host's immune system may become systemic and contribute to further deterioration of health. Severe progression may involve failure of the lung and other vital organs. Pneumonia with its high incidence, potentially severe course, and high mortality is one of the great medical challenges today. The German study groups PROGRESS, CAPNETZ, and SEPNET provide data and biomaterials from prospective, longitudinal studies. Partners bring clinical expertise, expertise in clinical studies, extensive experimental know-how, and many years of experience in mathematical modeling of biological systems to the consortium to enable a feedback-loop between mathematical modeling, verification of results in laboratory experiments, and detailed patient characterization - a systems medicine approach to better understand the course of pneumonia.

# Dynamical modelling of the murine immune response to pneumococcal lung infection with and without antibiotic treatment

Consortium CAPSyS

**Presenting Author: Peter Ahnert**

S. Schirm(1), P. Ahnert(1), M. Loeffler(1), M. Witzenrath(2), G. Nouailles(2), M. Scholz(1)

(1) Universität Leipzig, Institute for Medical Informatics, Statistics, and Epidemiology (IMISE), Leipzig, Germany (2) Charité - Universitätsmedizin Berlin, Department of Infectious Diseases and Respiratory Medicine, Berlin, Germany

Pneumonia is considered to be one of the leading causes of death worldwide. The outcome depends on both, proper antibiotic treatment and the effectivity of the immune response of the host. However, due to the complexity of the immunologic cascade initiated during infection, the latter cannot be predicted easily. We construct a biomathematical model of the murine immune response during infection with pneumococcus aiming at predicting the outcome of antibiotic treatment. The model consists on a number of non-linear ordinary differential equations describing dynamics of pneumococcal population, the inflammatory cytokine IL-6, neutrophils and macrophages fighting the infection and destruction of alveolar tissue due to pneumococcus. Equations were derived by translating known biological mechanisms and assuming certain response kinetics. Antibiotic therapy is modelled by a transient depletion of bacterials. Unknown model parameters were determined by fitting the predictions of the model to data sets derived from mice experiments of pneumococcal lung infection with and without antibiotic treatment. Time series of pneumococcal population, debris, neutrophiles, activated epithelial cells, macrophages, monocytes and IL-6 serum concentrations were available for this purpose. The antibiotics Ampicillin and Moxifloxacin were considered. Parameter fittings resulted in a good agreement of model and data for all experimental scenarios. Sensitivities of parameter estimates could be estimated. The model can be used to predict the performance of alternative schedules of antibiotic treatment. We conclude that we established a biomathematical model of pneumococcal lung infection in mice allowing predictions regarding the outcome of different schedules of antibiotic treatment. We aim at translating the model to the human situation in the near future.

# Operationalization of Disease Severity for Community Acquired Pneumonia of hospitalized Patients

Consortium CAPSyS

**Presenting Author: Peter Ahnert**

P. Ahnert(1), M. Scholz(1), F. Schwarzenberger(1), P. Creutz(2), M. Witzenrath(2), M. Löffler(1), N. Suttorp(2)

(1) Universitat Leipzig, Institute for Medical Informatics, Statistics, and Epidemiology (IMISE), Leipzig, Germany (2) Charite - Universitätsmedizin Berlin, Department of Infectious Diseases and Respiratory Medicine, Berlin, Germany

Community acquired pneumonia (CAP) is a common infectious disease with very high mortality world wide, commonly caused by Streptococcus pneumoniae. CAP is a major cause for hospital admission, especially among children and the elderly. Unfavorable outcomes may involve systemic inflammation, hypoperfusion, hypoxemia, and multi organ failure. For several decades, treatment has been relying mainly on timely administration of appropriate antibiotics. Besides a need for new treatment options, identification of patients with bad prognosis remains a challenge. Clinical or biomarkers of high predictivity would be useful to offer intensive care earlier to these patients. To this end, extensive observational trials are required, later followed by interventional trials. Such trials require an objective means for operationalization of disease severity from light to most severe, ideally a continuous score quantitatively describing the course of disease between patients of one study and between studies. It would be useful as a surrogate endpoint for disease outcome, for instance for the identification of potential biomarkers. Ideally, such a score could replace expert judgement for recognition of severe courses of disease. Currently available scores do not fulfil these requirements, partly because they were developed for outcome prediction at the time of hospitalization only. Within the CAPSyS consortium, we have further analyzed data collected by the “Pneumonia Research Network on Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis” (PROGRESS). Results suggest that the “Sequential Organ Failure Assessment” (SOFA) score may serve as an operationalization of CAP severity with the desired properties. Further analyses are required to determine if disease severity is adequately captured for patients with severely effected lungs but without involvement of extrapulmonal organs.

# Concerted T-cell activity against early and late BKV-antigens is necessary for viral clearance

Consortium e:Kid

**Presenting Author: Benjamin JD Weist**

Benjamin JD Weist2, Michael Schmück2, Mikalai Nienen2, Avidan Neumann2, Timm Westhoff, Prof. MD1, Petra Reinke, Prof. MD2 and Nina Babel, Prof. MD1,2.

1 Medical Clinic , Marien Hospital Herne, Ruhr University Bochum, Germany 2 Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charité Universitätsmedizin, Berlin.

Polyomavirus-BK (BKV) associated nephropathy is a known cause of graft failure. No specific therapy is established so far and viral load monitoring accompanied by adjustment of immunosuppression is the only known effective therapeutic option. We previously demonstrated BKV-specific T-cells as a factor predicting BKV-clearance and disease recovery. However, due to technical limitations, data on the role and specificity of different T-cell subsets including cytolytic/helper CD4 and CD8 T-cells is scarce and their specificity to early and late viral antigens is not defined. We implemented a multi-parameter flow cytometry protocol and investigated the sensitivity and robustness of variable effector molecules (IFN?, TNF?, IL2, IL4, IL17, GranzymeB) and receptors (4-1BB, CD40L, PD1) as BKV-specific activation markers under immunosuppression. By detecting BKV-specific T-cells according to the expression of the receptors CD137 and CD154 in combination with the effector molecule GranzymeB, we were able to detect specific T-cells more sensitively (compared to IFN?-based approaches) and categorized them into cytolytic/helper T-cells. Subsequently, antiviral immunity of 37 kidney transplant patients in clinical follow up and of 15 healthy volunteers was dissected into cytolytic and helper T-cell responses. Next, we dissected cytolytic and helper T-cell responses according to early and late BKV-antigen specificity. Our approach increased the sensitivity of detecting of BKV-specific T-cells by 4.2-fold (median) in comparison to previously used INF?-based detection by flow cytometry. Of importance, we showed that BKV clearance was observed when both, cytolytic and helper, T-cells were simultaneously detected. Interestingly, CD4 T-cells significantly contribute to viral clearance. Additionally we could assign Tbet driven CD4 T-cell responses to late BKV-antigens. By using surface markers together with the cytolytic molecule GranzymeB we showed for the first time a necessary concerted action of cytolytic and helper T-cells against early and late BKV-antigens. This new approach allows a more sensitive and reliable monitoring of BKV-specific T-cells. It can prevent underestimation of BKV-specific immunity and improve the adjustment of immunosuppression, minimizing the risk of graft rejection.

# A modeling framework for early stages in tertiary lymphoid organ formation after renal transplantation

Consortium SYSIMIT

**Presenting Author: Alexey Uvarovskii**

A. Uvarovskii (1), J. Dehghany (1), N. S. Schaadt (2), R. Schönmeyer (6), J.–H. Bräsen (2), S. Immenschuh (3), W. Gwinner (4), N. Krönke (2), F. Feuerhake (2), M. Meyer–Hermann (1,5)

(1) Department of Systems Immunology and Braunschweig Integrated Centre of Systems Biology, HZI, Germany (2) Institute for Pathology, Hannover Medical School, Germany (6) Definiens (3) Institute for Transfusion Medicine, Hannover Medical School, Germany (4) Clinic for Nephrology, Hannover Medical School, Germany (5) Institute for Biochemistry, Biotechnology and Bioinformatics, TU Braunschweig, Germany

Motivation: Tertiary lymphoid organs (TLO) are highly organized structures associated with chronic inflammation, including immune response to renal allografts. TLOs form distinct B and T cell zones with dendritic cells presenting antigens and a selection of B cells like in germinal center reactions. In animal models, TLO induction via injection of lymphatic tissue inducer (LTi) cells leads to higher risk of graft rejection. Understanding TLO development based on interdependency between model parameters and the probability of B cell cluster formation may help to prevent humoral components of renal allograft rejection. Mathematical modeling: Since perivascular stromal cells were shown to gain follicular dendritic cell phenotype upon contacts with B cells, we formulated a mathematical model of early B cell cluster formation in perivascular tissue, assuming that B cells enter the stroma with a certain frequency and activate perivascular cells to secrete the chemokine CXCL13. Its diffusion is described by a reaction-diffusion equation which is numerically solved on a grid. CXCL13 governs the combined chemotaxis and persistent random walk B cell movement and an increase of its concentration may lead to B cell clustering. Variable parameters which may rule the possibility and kinetics of TLO formation include frequency of B cell entrance, minimal contact time required for stroma differentiation, as well as signal decay rate, or mechanisms limiting interaction between stromal and B cells. Image Analysis: To validate and iteratively improve the mathematical model, we collected digital images of immunohistochemically stained renal biopsies which were taken at different time points after transplantation. Advanced image analysis tools were developed to identify, classify, and quantify relevant renal tissue compartments and cells. We used distance metrics reflecting interactions between epithelial and immune cells to inform parameters of the modeling framework. Results/Outlook: With the new modeling framework we reproduced cluster formation observed around perivascular tissue. Ongoing investigation of the dependency of cluster formation probability on the B cell influx rate is an important step towards the aim of this investigation, which is the determination of parameters in biopsies that allow judging the risk of TLO formation to optimize immunosuppressive therapy.

# A multiscale model of immune cell infiltration based on cyclic changes of epithelial cell turnover in the human breast to understand the role of lymphocytic lobulitis in oncogenesis

Consortium SYSIMIT

**Presenting Author: Juan Carlos A. Lopez**

J. C. A. Lopez (1), G. Apou (2), N. S. Schaadt (3), R. Schönmeyer (4), B. Auber (5), G. Forestier (6), N. Krönke (3) , C. Wemmert (2), F. Feuerhake (3), H. Hatzikirou (1)

(1) Center for Advancing Electronics (cfAED), Technische Universität Dresden, Germany (2) ICube (Image Analysis & Computational Science Laboratory), Université de Strasbourg, France (3) Institute of Pathology, Hannover Medical School, Germany (4) Definiens AG, Munich, Germany (5) Institute of Human Genetics, Hannover Medical School, Germany (6) MIPS (Modélisation, Intelligence, Processus et Systèmes), Université de Haute-Alsace, Mulhouse, France

Motivation: The goal is improved understanding of the role lymphocytic lobulitis (LLO), a recurrent inflammation pattern in hereditary breast cancer (hBC). Currently, the LLO definition is purely descriptive and it is unclear if it is a physiological process or an indication of pathology. To delineate the role of LLO, we initially investigate recurrent inflammation during physiological menstrual cycles. In turn, we systematically analyze system perturbations that may lead to oncogenic events. Mathematical modeling: We developed a cell-based model that reflects the interactions between immune and epithelial cells with normal cell turnover rates during the menstrual cycle. Physiological model parameters are calibrated based on comprehensive spatial data extracted from digital whole-slide images (WSI) of immunohistochemical epithelial, vascular, and immune cell markers, based on material and clinical annotation from 53 healthy patients who underwent reduction mastectomy for aesthetical or orthopedic indications. The model allows for the qualitative and quantitative analysis of lobular inflammation patterns under systematic parameter perturbations, such as increased cell turnover rates, impaired DNA-repair mechanisms due to BRCA1/2 mutations, or decreased efficiency of effector immune cells. Image Analysis: We established a modular workflow combining a convolutional neural network (CNN) to detect regions of interest (ROI) with a novel technology for robust nucleus detection (“nucleus container” module; Definiens, Germany). These advanced immune cell analyses result in the quantitative read–out required to parameterize, validate, and iteratively improve our mathematical model. Results: Associated with hormonal fluctuations during the menstrual cycle, normal breast lobules can temporarily be invaded by high numbers of immune effector cells. Therefore, we propose a dynamic definition of LLO beyond immune cell density. Moreover, we show differences between inflammatory patterns observed in tissues from healthy and BRCA mutated patients. Vision: We anticipate that improved disease understanding of LLO will contribute to the extension of criteria for hBC biopsy evaluation, the development of novel prognostic markers, and new perspectives for immunomodulatory therapeutic interventions. The modular workflow is being expanded to applications in biopsies of prophylactically removed breast tissue of patients with BRCA1/2 mutations, and in cancer.

# Genome-wide Comparative Analysis of Atopic Dermatitis and Psoriasis Gives Insight into Antagonistic Genetic Mechanisms

Consortium SysINFLAME

**Presenting Author: Hansjörg Baurecht**

Hansjörg Baurecht 1, Melanie Hotze 1, Jorge Esparza-Gordillo 2, Regina Fölster-Holst 1, Andre Franke 3, Christian Gieger 4, Alan D. Irvine 5, Michael Kabesch 6, Young A.E. Lee 7, Wolfgang Lieb 8, W.H. Irwin McLean 9, Rajan Nair 10, Natalija Novak 11, Konstantin Strauch 12, Richard Trembath 13, Jonathan Barker 13, James T. Elder 10, Stephan Weidinger 1, Heather J. Cordell 14,?Sara J. Brown 15

1 Department of Dermatology, Allergology, and Venereology, University Hospital Schleswig-Holstein, Kiel, Germany. 2 Max-Delbrück-Centrum (MDC) for Molecular Medicine, Berlin, Germany. 3 Institute of Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany. 4 Research Unit of Molecular Epidemiology, German Research Center for Environmental Health, Neuherberg, Germany. 5 Department of Paediatric Dermatology, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland. 6 Department of Pediatric Pneumology and Allergy, University Children's Hospital Regensburg (KUNO), Regensburg, Germany. 7 Pediatric Allergy, Experimental and Clinical Research Center, Charite ?, Berlin, Germany. 8 Institute of Epidemiology and PopGen Biobank, University Hospital Schleswig-Holstein, Kiel, Germany. 9 Dermatology and Genetic Medicine, College of Life Sciences and College of Medicine, Dentistry & Nursing, University of Dundee, Dundee, UK. 10 Department of Dermatology, University of Michigan, Ann Arbor, Michigan, USA. 11 Department of Dermatology and Allergy, University of Bonn Medical Center, Bonn, Germany. 12 Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany. 13 Queen Mary University of London, Barts and the London School of Medicine and Dentistry, London, UK. 14 Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK; 15 Dermatology and Genetic Medicine, Medical Research Institute, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK.

Background: Atopic dermatitis (AD) and psoriasis are common chronic inflammatory skin diseases, which despite their prevalence rarely co-exist within the same patient, reflecting mutually exclusive immunological features. Methods: We utilized genome-wide association study and ImmunoChip data from more than 19,000 individuals and applied analytical approaches based on meta-analysis techniques. Results: We identified antagonistic risk alleles at shared loci as well as independent disease-specific loci within the epidermal differentation complex on 1q21.3, the cytocine cluster on 5q31.1, and the major histocompatibility complex on 6p21-22. We further indentified previously unreported pleiotropic loci with antagonistic effects on AD and psoriasis (PKKRA and ANXA6/TNIP1). In contrast, there was no evidence for agonistic loci. Conclusion: Our results show that AD and psoriasis have distinct genetic mechanisms with antagonistic effects in shared pathways influencing epidermal differentiation and immune response. The statistical analysis methods developed in the conduct of this study have revealed additional insight from previously published data sets. The approach can be transferred to investigation of the genetic basis of other complex disorders with related and distinct clinical features.

# Epidemiologic and genetic association between atopic dermatitis, rheumatoid arthritis, inflammatory bowel disease, and type-1 diabetes

Consortium sysINFLAME

**Presenting Author: Hansjörg Baurecht**

H Baurecht 1, J Schmitt 2, E Rodriguez 1, C Gieger 3, A Irvine 4, N Novak 5, W Lieb 6, and S Weidinger1

Department of Dermatology, Venereology and Allergy, University Hospital Schleswig-Holstein, Kiel, Germany, 2 Center for Evidence-based Healthcare, Medizinische Fakultät Carl Gustav Carus, TU Dresden, Dresden, Germany, 3 Institute of Genetic Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany, 4 Department of Paediatric Dermatology, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland, 5 Department of Dermatology and Allergy, University of Bonn, Bonn, Germany and 6 Institute of Epidemiology and PopGen Biobank, University Hospital Schleswig-Holstein, Kiel, Germany

Atopic dermatitis (AD) is characterized by epidermal barrier failure and cutaneous inflammation. Molecular studies suggested shared genetic factors and immunological pathways with other inflammatory diseases as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), but epidemiological evidence is scarce. We test the hypothesis that prevalent AD is a risk factor for incident RA and IBD and inversely related to type-1 diabetes (T1D) and investigate RA, IBD, and T1D susceptibility loci in AD. This cohort study utilized data from German National Health Insurance beneficiaries age 40 or younger (n=655,815) from 2005 through 2011. Prevalent AD in 2005/2006 was defined as primary exposure, and incident RA, IBD, and T1D in 2007–2011 as primary outcomes. Risk ratios were calculated and established RA, IBD and T1D loci were explored in high density genotyping data. Patients with prevalent AD were at increased risk for incident RA (risk ratio (RR) 1.72, 95%CI=1.25–2.37), CD (RR 1.34, 95%CI=1.11–1.61) and UC (RR 1.25, 95%CI=1.03–1.53). There was no disproportionate occurrence of known RA, CD, UC or T1D risk alleles in AD. AD is a risk factor for the development of RA and IBD. The excess comorbidity cannot be attributed to major known IBD and RA genetic risk factors.

# Biological therapies and intestinal microbiota: A longitudinal study in diverse disease phenotype

Consortium SysINFLAME

**Presenting Author: Ateequr Rehmann**

Ateequr Rehman, Konrad Aden1,2, Berenice Brandt2, Johannes Bethge2, Susanna Nikolaus2,, Oltmann Schroeder1, Stefan Schreiber1,2 and Philip Rosenstiel1

1 Institute of Clinical Molecular Biology, Christian-Albrechts-University and University Hospital Schleswig-Holstein, Campus Kiel, 24105 Kiel, Germany 2 First Medical Department, Christian-Albrechts-University and University Hospital Schleswig-Holstein, Campus Kiel, 24105 Kiel, Germany

Background: Immune modulating recombinant antibodies (such as anti TNF antibodies) are the most effective therapies for a broad and heterogeneous group of disease including rheumatoid arthritis and inflammatory bowel disease. Pathogenesis of these diseases is argued around microbial driven activation of immune cascade and cytokine imbalance; however impact of such targeted cytokine blockade on intestinal microbial communities is poorly understood. Aim: This study aims to determine the impact of biological therapies on microbiota in patient cohort from intestinal and non intestinal diseases. Method: We enrolled rheumatoid and inflammatory bowel disease patients for this longitudinal study. Healthy volunteer without any known disease served as control group. Fecal samples were collected on the start of therapies and on 1 day, 3 day, 1 week, 1 month and 6 months of therapeutic interventions. DNA was extracted from fecal samples and V4 region of the 16S rRNA gene was sequenced using Mieq Illumina platform. Results: We observed significant differences in the proportion of major bacterial groups (Firmicutes and Actinobacteria) after biological therapies. Likewise microbial composition and structure (beta diversity) was significantly altered after therapy if compared to the changes in healthy volunteers within same time frame. We are now linking these therapeutic associated microbial changes to the predicated microbial metabolic profiles; results will be presented at the conference. Conclusion: Our data suggests a marked influence of biological therapies on microbial composition and structure.

# NK cells as biosensors for responsiveness to Etanercept in ankylosing spondylitis (Morbus Bechterew)

Consortium SysINFLAME

**Presenting Author: Ursula Schulte-Wrede**

Ursula Schulte-Wrede, * Till Sörensen, Joachim R. Grün, * Joachim Sieper, * Thomas Häupl, Andreas Radbruch, Andreas Grützkau

German Rheumatism Research Center Berlin (DRFZ), an Institute of the Leibniz-Association, Immune-Monitoring Core Facility, Berlin, Germany; * Charité Universitätsmedizin der HU-Berlin, Department of Rheumatology and Clinical Immunology, Berlin, Germany

Background: Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease which preferentially affects the axial skeleton and is strongly associated with the pro-inflammatory cytokine tumor necrosis factor alpha (TNF). Therapeutic targeting of TNF is approved to be highly effective in patients who fail to respond to conventional anti-inflammatory drugs. However, only around two-thirds of anti-TNFa treated AS patient's shows an adequate response according to the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) independently from the biological used. Therefore, there is an urgent need for biomarkers which would aid in treatment choice and treatment outcome separating responders and non-responders to such expensive therapies and to avoid side effects induced by inefficient drugs. . Thus, the aim of this study was to identify cell-based biosensors in peripheral blood by multiparametric flow cytometry that can be used for an early treatment stratification of AS patients. Methods: A multiparametric flow cytometric approach, including 50 monoclonal antibodies combined to 10 staining cocktails, was applied to identify useful baseline predictors in 38 AS patients with active disease before treatment with the TNF blocker Adalimumab, Etanercept, Golimumab or Infliximab. BASDAI response criteria were used to determine therapeutic success after 1 to 6 month. Automated clustering of flow data, correlation analysis and receiver operator characteristics were accomplished to appoint auspicious candidate phenotypes. Results: Out of multiple potentially significant parameters, which are involved both in acquired and adaptive immunity the NK cell compartment revealed most promising subsets that are predictive for a successful therapy response to Etanercept in AS. Correlation analyses showed an errorfree classification of responders and non-responders for Etanercept but not for Adalimumab-treated patients. Conclusions: This is the first study demonstrating that the composition of the NK cell compartment has predictive power with respect to classify AS patients whether they will respond or fail to the treatment by Etanercept. These results also shed some new light on the mode of action comparing TNF-alpha neutralizing antibodies and soluble TNF alpha-receptors. In conclusion, these data make it reasonable to assume that monitoring of particular NK cell phenotypes can be used in terms of a companion diagnostic to realize the concept of personalized medicine in the field of rheumatology. But we are aware that the results presented have to be validated by independent and larger patient cohorts.


# Poster Presentations
# VIII ELSA on Systems Medicine

# DASYMED: Big Data in Systems Medicine. Normative and Social Aspects for Physicians, Scientists, Patients and Society

DASYMED

**Presenting Author: Christoph Schickhardt**

Sandra Fernau, Henrike Fleischer, Sebastian Schleidgen, Christoph Schickhardt, Jochen Taupitz, Eva Winkler

Institute for German, European and International Medical Law, Public Health Law and Bioethics (IMGB), Ruprecht-Karls-University of Heidelberg and University of Mannheim Department of Medical Oncology, National Center for Tumor Diseases (NCT), Program "Ethics and Patient-oriented Care in Oncology (EPOC), Heidelberg University Hospital

The focus of DASYMED is twofold: first, we examine changes of ascribed responsibilities of physicians and researchers in systems medicine. Second, we address questions emerging from data-driven research with respect to the balancing of the subjects' privacy and social benefit. With regard to the focus on responsibilities, we undertake three socio-empirical research steps: 1. a direct participant observation in a molecular tumor conference at the NCT; 2. guideline-based interviews with physicians and researchers; and 3. an analysis of a focus group interview study with patients. Based on the study results as well as a review of the philosophical literature on the concept of responsibility and the history of the biomedical research ethos, we conduct an ethical analysis of possible new responsibilities in systems medicine. Furthermore, the legal rights and obligations of patients, research participants, physicians, and researchers are investigated. So far, several problems resulting from applying the German Genetic Diagnostics Act (GenDG) in systems medicine have been identified and the limits of regulations concerning genetic data have been specified. With regard to balancing privacy and research benefit, a qualitative interview study on the subjective perceptions, opinions and attitudes of patients and physicians regarding threats to privacy resulting from data sharing in genomic research is in its final stages. The results of this study will serve as the basis for the ethical analysis of questions concerning the patients' privacy in the context of systems medicine. Moreover, a paper was compiled, which discusses the question of whether or not genetic raw data should be disclosed to patients or research participants.

# Online Availability of Guidelines and Policies about Acquiring, Storing and Processing Epigenetic Data in Systems Medicine

EDEA

**Presenting Author: Katharina Viktoria Röntgen**

Katharina Viktoria Röntgen (1), Jens Clausen (1), Hans-Jörg Ehni (1), Thomas Potthast (2), Urban Wiesing (1)

(1) Institute of Ethics and History of Medicine, University Hospital Tuebingen, Tuebingen, Germany
(2) International Centre for Ethics in the Sciences and Humanities (IZEW), Tuebingen, Germany

Within the scope of our project on the international practices of handling epigenetic data, we examined easy online availability of policies and guidelines, on websites of universities, autonomous institutes, companies and project consortia dealing with epigenetic data in Germany, Europe and the US. Methods: Our sample of web-addresses was collected by two independently acting internet users, following a prior set browsing-strategy. Resulting websites were pooled and analyzed. They were quantified considering location, type, and availability of guidelines and policies. Found documents were qualitatively analyzed regarding their purpose: if fulfilling demands of patients and donors (non-specialists) or researchers, respectively. Additionally we examined if there was explicit reference to epigenetic data. Results: The sample contained 95 websites, split in 41.1 % university institutes, 32.6 % autonomous institutes, 16.8 % companies, 9.5 % project consortia. Over all, we found that 29.4 % of our sample had policies and guidelines easily available online. Sorted by type, availability was best (55.5 %) at the project consortia and lowest at company sites (18.8 %). Evaluated by location, availability was significantly low on German websites (17.9 %), compared to the rest of Europe and the US (37.5 % each). Contextual, qualitative analysis of the documents revealed that the majority was focused on the data protection requirements of the scientific community, while only a few were addressing non-specialists. In three cases we found explicit reference to epigenetic data. Best non-specialist availability was found on websites of large scale biobanks and epidemiological project consortia. Discussion: While it is inevitable to share data to enable progress in Systems Medicine, all involved stakeholders have legitimate interest in data protection as well. In respect to participating non-specialists, it is also important to make aims and procedures of research understandable on a non-professional level. Our results clearly show that stakeholder-friendly online availability of research policies and guidelines is proportionally low up to now. Regarding the importance of internet use in the information society the availability rate seems insufficient. It is even more inadequate considering the needs of non-specialists. Epigenetic data or testing is very rarely addressed at all, which is questionable, considering the current prioritization of epigenetic research in Systems Medicine.

# Regulating the access to material and data stored in biobanks. Findings from a thematic analysis of international access policies

FairBBank

**Presenting Author: Holger Langhof**

Holger Langhof, Hannes Kahrass, Sören Sievers, Prof. Dr. Dr. Daniel Strech

Medizinische Hochschule Hannover (MHH) Institut für Geschichte, Ethik und Philosophie der Medizin CELLS - Centre for Ethics and Law in the Life Sciences Carl-Neuberg-Str. 1 30625 Hannover

Background Human biological materials (HBM) and the associated data stored in international biobanks are highly valuable resources for systems medicine, especially if it allows for networked national and international research. Biobank specific access policies (AP) specify the governance of HBM and data sharing. Basic guidance for the formulation of AP exists, but so far only little is known about the current practice of AP in international biobanks. Objectives To analyse the full spectrum of criteria and procedures presented in AP from international biobanks; including a particular look at criteria and procedures for priority setting in access decisions on scarce samples. Methods AP were gathered by: (i) Mail-survey, targeting all biobanks listed in the BBMRI-catalogue; (ii) web-search for AP of non-respondents to the Mail-survey; (iii) web-search for biobank AP of other international biobank networks; (iv) google-search for additional biobanks. APs from 80 biobanks were collated and thematic analysis was applied. Results There is a broad variety of criteria applied to regulate access, among others several issues around quality, scientific value or the ethical soundness of the planned research. Procedures as well are very heterogenous, e.g. biobank-internal responsibilities for access decisions or processing of applications. Priority setting is often not specified explicitly. Discussion/Conclusion Criteria and procedures for access and priority setting in biobank research need to be (as best as possible and feasible) precise and transparent in order to allow for the best use of the valuable resources. Several stakeholders, such as the German TMF working group on biobanks, expressed a significant interest on this topic. Further research will address this need (e.g. international survey with biobank stakeholders) and develop a best practice model for AP formulation and design, including the issue of priority setting.

# GenoPerspektiv – Managing Genomic High-Throughput Data: Regarding the Perspectives of the Clinic, Biomedical Information Technology, Ethics, and Law

GenoPerspektiv

**Presenting Author: Nadine Umbach**

Nadine Umbach (1), Tim Beißbarth (2), Gunnar Duttge (3), Laura Flatau (4), Jochen Gaedcke (5), Sebastian Kunze (1), Juliane Kathleen Linke (3), Benjamin Löhnhardt (6), Julia Perera Bel (2), Markus Reitt (4), Julia Roschauer (3), Silke Schicktanz (7), Thomas G Schulze (8), Mark Schweda (7), Alexander Urban (7), Anja Zimmermann (3), Ulrich Sax (1)

(1) Department of Medical Informatics, University Medical Center Göttingen, Göttingen, Germany (2) Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany (3) Center for Medical Law, Göttingen University, Göttingen, Germany (4) Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany (5) Department of General and Visceral Surgery, University Medical Center Göttingen, Göttingen, Germany (6) Operational Division of Information Technology (G3-7), University Medical Center Göttingen, Göttingen, Germany (7) Department of Medical Ethics and History of Medicine, University Medical Center Göttingen, Germany (8) Institute for Psychiatric Phenomics and Genomics, Ludwig-Maximilian-University Munich, Germany

Genomic high-throughput technologies (gHTT) enables deep insights into genotype-phenotype correlations of individuals that underlie many human diseases. In the last years, the advent of highly efficient and cost-effective techniques has expanded its scope of application from research into clinical practice. However, the growing popularity of gHT is also accompanied by big challenges. The increasing volume of huge and highly complex data sets poses difficult problems regarding data collection, processing, interpretation, and protection. The large pool of sensitive information remains difficult to interpret and many ethical, social, and legal issues, e.g. regarding informed consent and privacy, are still in need of clarification. Moreover, suitable infrastructures to deal with the ever-increasing amount and complexity of data are not yet established. Against this background, in GenoPerspektiv, an interdisciplinary team of medical ethicists, medical lawyers, physicians, statisticians, and computer scientists addresses the following major research objectives: (1) development of concepts for reporting and visualization of data from gHTT in clinical routine; (2) development of strategies for a sustainable and traceable data management (including annotation, archiving, and provision of data), long-lasting infrastructure as well as organizational frameworks in both research and clinical context; (3) exploration of ethical implications of gHTT for informed consent procedures through qualitative social research and ethical analysis; (4) investigation of public attitudes towards gHTT and identification of needs and concerns regarding the confrontation with genetic test results; (5) analysis of legal issues with a particular focus on the German Gene Diagnostics Act, protection of data privacy, as well as on medical malpractice and health insurance laws. From a legal perspective the handling of genomic high-throughput technologies raises a variety of issues.

Of great importance in this context are the scope of the consent of the person concerned in the context of self-determination and the" right not to know" of the person concerned regarding the so-called "incidental findings". The project furthermore focuses on the question whether or not medical confidentiality and data protection can still be guaranteed given the increase of genetic data. In addition new questions arise in the context of medical liability as well as the classification of (predictive) genetic testing in the system of compulsory health insurance. GenoPerspektiv aims at defining medical and bioinformatical, ethical, psycho-social, and legal recommendations, guidelines, strategies, and concepts on how to manage data from gHTT. The gained findings are developed and disseminated in close dialogue with the public, patients and their relatives, and professionals of the health care system. The results of the first working packages indicate, that some challenges we are facing are not unique to our project. So we successfully contributed to the e:Med project group on privacy and ethics in both fields. Conducting interviews in various institutions and with several experts in the field already raised the awareness for our area of research. Recently a GenoPerspective invited, highly visible keynote lecture by Prof. Benedikt Brors focused on the necessity of meaningful reports on high throughput data in the German Medical Informatics Association (GMDS).

# Systems Medicine – A current Approach in Medicine and its Ethical and Economic Challenges

MENON

**Presenting Author: Tobias Fischer**

Tobias Fischer (1), Susan Raths (2), Pia Erdmann (3), Steffen Fleßa (2), Martin Langanke (3)

(1) University Medicine Greifswald, Department of Ethics, Theory and History of Life Sciences (2)Ernst Moritz Arndt University Greifswald, Faculty of Law and Economics, Department of Health Care Management (3)Ernst Moritz Arndt University Greifswald, Faculty of Theology, Department of Systematic Theology

Current systems medicine is not a homogenous approach, but a field of methodologically differentiable concepts, which is held together by the topic “IT and data management”. Therefore ethical and economical questions regarding chances and risks of systems medicine cannot be asked globally the systems medicine. Only selected branches within systems medicine can be ethically and economically assessed. From an ethical point of view the use and implementation of big data based scores in the health care context as well as the handling of unsolicited findings seem to be major challenges. From a health economic perspective it is relevant, whether systems medicine will lead to higher revenues for health care providers or only to higher costs which cannot be recovered.

# Concepts and Meanings of Integration in Systems Medicine

ModMen

**Presenting Author: Regine Kollek**

Regine Kollek, Imme Petersen

Universität Hamburg, Research Centre for Biotechnology, Society and the Environment

The application of high-throughput technologies in systems medicine has led to a plethora of heterogeneous data on biological processes, including gene expression, metabolism and signaling. This has brought new urgency to the problem of how to deal with the large volume of data of different types, stored in separate databases and located at different geographical sites. Indeed, integration of data coming from such autonomous databases raises serious questions concerning data protection and audited data access. However, also basic epistemic problems have been identified with regard to the circumstances the data were collected (e.g., context of application, history of data collection, local institution, national law) and to different terminology and classification systems used by different databases. Furthermore, the heterogeneity of data gathered at different levels of biological complexity is a major challenge in data analysis. To build multilayer disease modules, large and heterogeneous data of disease-related information (e.g., genotype, phenotype, environmental factors) are correlated. Therefore, a great deal of attention has been put on data integration, primarily to retrieve and combine large, heterogeneous datasets into standardized and incorporated forms and structures. However, this data-centred concept of integration is contrary to the philosophical debate on integration that rather emphasizes the dynamics and contexts of integration processes. These differences between the concepts and meanings of integration in systems medicine and philosophy are explored to get a deeper insight into the integration processes in systems medicine.

# Systems Medicine in the Prevention of Mental Disorders – A legitimate Approach?

SysKomp

**Presenting Author: Pauline Mantell, Marc Jannes**

Pauline Mantell (1), Marc Jannes (1), Christiane Woopen (1)

(1) Research Unit Ethics, University Hospital Cologne, Germany

Mental disorders often cause enormous burden on affected individuals, their families and society. The World Health Organization considers the prevention of mental disorders among their most important future tasks. Systems medicine provides access to an increased number of new scientific data sources as a basis for innovative possibilities of data analysis. This promises to bring about the long desired paradigm shift towards prevention in the mental health care system by developing more effective early detection, prevention and treatment strategies. However, this promising approach goes along with ethical concerns which have to be considered. The theoretical analysis of challenges for systems medicine in the context of prevention of mental disorders is based on the conceptual framework by the Institute of Medicine which consists of three prevention categories: The universal approach refers to the general population, the selective one to persons at risk as well as indicated preventive measures for those who show initial symptoms which in themselves do not yet constitute a diagnosable mental disorder. The use of systems medicine in the context of prevention of mental disorders arouses ethical concerns related to autonomy, privacy, justice and nonmaleficence in all of the three preventive categories. With regard to prevention measures of mental disorders, it becomes especially challenging since people with mental distress might already suffer from cognitive difficulties. These can lead to incomplete knowledge, misinterpretations, and misunderstandings. Information on potential risks of mental disorders present especially sensible data since mental disorders often go along with stigmatization and discrimination. It is essential to find a way to contain and deliver high informational data in mental health prevention in a meaningful way. On the other hand, systems medicine can promote a more holistic view on mental health, which has long been called for from an ethical point of view.

# SYSKON. Re-configuration of health and disease. Ethical, psychosocial, legal and health economic challenges of systems medicine: The case of hereditary breast cancer.

SYSKON

**Presenting Author: Friedhelm Meier**

Peter Dabrock, Stefan Huster, Jürgen Wasem, Rita Schmutzler

Prof. Peter Dabrock: Chair of Systematic Theology II (Ethics) at the Friedrich-Alexander University Erlangen-Nürnberg, Prof. Dr. Stefan Huster: Institute of Social Law and Health Law at the Ruhr University of Bochum, Prof. Dr. Jürgen Wasem: Institute for Health Services Management and Research at the University Duisburg-Essen, Prof. Dr. Rita Schmutzler: Department of Obstetrics and Gynecology, Division Molecular Gyneco-Oncology at the University of Cologne

Background and over-all objectives: Referring to hereditary breast cancer as a paradigmatic case, SYSKON investigates challenges and chances of systems medicine, especially consequences for clinical care and the health care system in general. The consortium aims at developing an integrative matrix of benchmarks for the governance of the identified opportunities and limitations. Structure: SYSKON comprises five subprojects: Administration (SP1, Erlangen), Ethics (SP2, Erlangen), Medicine (SP3, Cologne), Law (SP4, Bochum) and Health Economics (SP5, Duisburg-Essen). First year's activities: SYSKON developed and published a concise interdisciplinary research account, established a studies platform integrating stakeholders like health insurances and patient support groups and held public events and lectures. Current activities: Systems medicine tends to blur the distinction between health and disease. SYSKON investigates the „healthy ill" concept with regard to the case of hereditary breast cancer. Practical effects of this obscuring of concepts can be observed in the legal frame of the health care system as a growing part of the consequences of systems medicine on health care and genetic diagnosis are not properly covered by the established law. Finally, the systems medicine's ramifications for the health care budget are far from clear and are, therefore, investigated by SYSKON with regard to different scenarios. Beside more or less theoretical accounts, two empirical studies are conducted dealing with patients' and families' attitudes toward BRCA 1/2 testing and preventive options. First results indicate that psychological parameters like anxiety and depression scores influence the demand for invasive measures and affect the process of decision-making to a great extent. Perspectives: SYSKON will combine the interim results and will initiate the preparing of a governance model dealing with the ethical, psychosocial, legal and economic consequences of systems medicine.


# List of e:Med
# Systems Medicine Research Consortia

**CancerTelSys**

Identifying cancer Telomere maintenance networks for diagnosis, prognosis, patient stratification and therapy response prediction

Coordinator: PD Dr. Karsten Rippe

| **Coordinator of subproject** | | | | **Subproject** | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Plass | Christoph | Prof. Dr. | Deutsches Krebsforschungszentrum (DKFZ) Heidelberg | SP1 | TMM-Marker des Genoms, Epigenoms und Transkriptoms |
| König | Rainer | Prof. Dr. | Center for Sepsis Control and Care (CSCC), Universitätsklinikum Jena | SP1 | TMM-Marker des Genoms, Epigenoms und Transkriptoms |
| Luke | Brian | Dr. | Universität Heidelberg | SP1 | TMM-Marker des Genoms, Epigenoms und Transkriptoms |
| Pfister | Stefan | Prof. Dr. med. | Deutsches Krebsforschungszentrum (DKFZ) Heidelberg | SP1 | TMM-Marker des Genoms, Epigenoms und Transkriptoms |
| Sauter | Guido | Prof. Dr. med. | Universitätsklinikum Hamburg-Eppendorf | SP1 | TMM-Marker des Genoms, Epigenoms und Transkriptoms |
| Simon | Ronald | Dr. | Universitätsklinikum Hamburg-Eppendorf | SP1 | TMM-Marker des Genoms, Epigenoms und Transkriptoms |
| Rohr | Karl | Prof. Dr. | Universität Heidelberg | SP2 | Bildanalyse zytologischer TMM-Merkmale |
| Erfle | Holger | Dr. | Universität Heidelberg | SP2 | Bildanalyse zytologischer TMM-Merkmale |
| König | Rainer | Prof. Dr. | Center for Sepsis Control and Care (CSCC), Universitätsklinikum Jena | SP3 | Modellierung von TMM-Netzwerken in Tumoren |
| Luke | Brian | Dr. | Universität Heidelberg | SP3 | Modellierung von TMM-Netzwerken in Tumoren |
| Rippe | Karsten | PD Dr. | Deutsches Krebsforschungszentrum (DKFZ) Heidelberg | SP3 | Modellierung von TMM-Netzwerken in Tumoren |
| Rohr | Karl | Prof. Dr. | Universität Heidelberg | SP3 | Modellierung von TMM-Netzwerken in Tumoren |
| Rippe | Karsten | PD Dr. | Deutsches Krebsforschungszentrum (DKFZ) Heidelberg | SP4 | Validierung und funktionelle TMM-Analyse |
| Erfle | Holger | Dr. | Universität Heidelberg | SP4 | Validierung und funktionelle TMM-Analyse |
| Luke | Brian | Dr. | Universität Heidelberg | SP4 | Validierung und funktionelle TMM-Analyse |
| Pfister | Stefan | Prof. Dr. med. | Deutsches Krebsforschungszentrum (DKFZ) Heidelberg | SP4 | Validierung und funktionelle TMM-Analyse |
| Plass | Christoph | Prof. Dr. | Deutsches Krebsforschungszentrum (DKFZ) Heidelberg | SP4 | Validierung und funktionelle TMM-Analyse |

**CancerTelSys**

Identifying cancer Telomere maintenance networks for diagnosis, prognosis, patient stratification and therapy response prediction

Coordinator: PD Dr. Karsten Rippe

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Erfle | Holger | Dr. | Universität Heidelberg | SP5 | Technologieentwicklungen zur TMM-Klassifizierung |
| Luke | Brian | Dr. | Universität Heidelberg | SP5 | Technologieentwicklungen zur TMM-Klassifizierung |
| Rippe | Karsten | PD Dr. | Deutsches Krebsforschungszentrum (DKFZ) Heidelberg | SP5 | Technologieentwicklungen zur TMM-Klassifizierung |
| Pfister | Stefan | Prof. Dr. med. | Deutsches Krebsforschungszentrum (DKFZ) Heidelberg | SP6 | Klinische Anwendung des TMM-Analyseschemas |
| Luke | Brian | Dr. | Universität Heidelberg | SP6 | Klinische Anwendung des TMM-Analyseschemas |
| Plass | Christoph | Prof. Dr. | Deutsches Krebsforschungszentrum (DKFZ) Heidelberg | SP6 | Klinische Anwendung des TMM-Analyseschemas |
| Rippe | Karsten | PD Dr. | Deutsches Krebsforschungszentrum (DKFZ) Heidelberg | SP6 | Klinische Anwendung des TMM-Analyseschemas |
| Sauter | Guido | Prof. Dr. med. | Universitätsklinikum Hamburg-Eppendorf | SP6 | Klinische Anwendung des TMM-Analyseschemas |
| Rippe | Karsten | PD Dr. | Deutsches Krebsforschungszentrum (DKFZ) Heidelberg | SPC | Koordination |

**CAPSyS**

Medical Systems Biology of Pulmonary Barrier Failure in Community Acquired Pneumonia

Coordinator: Prof. Dr. Markus Löffler

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Löffler | Markus | Prof. Dr. | Universität Leipzig: Institut für Medizinische Informatik, Statistik und Epidemiologie (IMISE) | TP 1 und TP 5 | Integrative genetische Analyse und Biomathematische Modellierung der Systemischen Entzündung (TP 1) und Datenintegration, Datamining und Projektmanagement (TP 5) |
| Suttorp | Norbert | Prof. Dr. | Charité - Universitätsmedizin Berlin | TP 2 und TP 4 | "Deep phenotyping"-Kohorte, neue Analysen (TP 2) und Experimentelle Modellierung und Validierung der Pathophysiologie der Pneumonie (TP 4) |
| Vera-Gonzalez | Julio | Prof. Dr. | Friedrich-Alexander-Universität Erlangen-Nürnberg | TP 3 | Mathematische Modellierung der Pathophysiologie der Lungenentzündung |
| Schmeck | Bernd T. | Prof. Dr. | Philipps-Universität Marburg | TP 4 | Experimentelles Modelling und Validierung der Pathophysiologie der Pneumonie |

## CLIOMMICS

Clinically-applicable, omics-based assessment of survival, side effects, and targets in multiple myeloma

Coordinator: Prof. Dr. Hartmut Goldschmidt

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Knaup | Petra | Prof. Dr. | Institute for Medical Biometry and Informatics (IMBI) | B1.1 | Multi-level data management and IT architecture for systems medicine for multiple myeloma |
| Hemminki | Kari | Prof. Dr. | German Cancer Research Center (DKFZ) | B2.1 | Genetic markers predicting side effects, therapeutic response and prognosis in myeloma |
| Hose | Dirk | PD Dr. | Universitätsklinikum Heidelberg, Med. Klinik V Labor für Myelomforschung | B3.1 | Transcriptomics by RNA-sequencing: Performing and reporting in clinical routine |
| Seckinger | Anja | Dr. | Universitätsklinikum Heidelberg, Med. Klinik V Labor für Myelomforschung | B3.1 | Transcriptomics by RNA-sequencing: Performing and reporting in clinical routine |
| Kopp-Schneider | Annette | Prof. Dr. | German Cancer Research Center (DKFZ) | B4.1 | Combining SNPs, iFISH, GEP/RNA-seq, and MRI in improving risk prediction and treatment decisions making |
| Hielscher | Thomas | Dipl.-Statistiker | German Cancer Research Center (DKFZ) | B4.1 | Combining SNPs, iFISH, GEP/RNA-seq, and MRI in improving risk prediction and treatment decisions making |

## e:Athero-Sysmed

Systems medicine of myocardial infarction and stroke

Coordinator: Prof. Dr. Jeanette Erdmann, Prof. Dr.Heribert Schunkert

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| König | Inke R. | Prof. Dr. | Universität zu Lübeck, Institut für Medizinische Biometrie und Statistik | 1 | Identifikation von Risikoallelen und Risikoprofilen |
| Müller-Myhsok | Bertram | Prof. Dr. | Max-Planck-Institut für Psychiatrie, Research Group Statistical Genetics | 1 | Identifikation von Risikoallelen und Risikoprofilen |
| Peters | Annette | Prof. Dr. | Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH), Institute of Epidemiology II | 2, 4 | Systemmedizinische OMICs-Analysen bei koronaren Herzerkrankungen in Kohortenstudien (TP2), SNP-vermittelte (Dys)Regulation in der Atherosklerose (TP4) |
| Söding | Johannes | Dr. | Max-Planck-Institut für biophysikalische Chemie | 3 | Identifikation krankheitsassoziierter genregulatorischer Netzwerke |
| Engelhardt | Stefan Hanns | Prof. Dr. | Technische Universität München, Institut für Pharmakologie und Toxikologie | 4 | SNP-vermittelte (Dys)Regulation in der Atherosklerose |

## e:Athero-Sysmed

Systems medicine of myocardial infarction and stroke

Coordinator: Prof. Dr. Jeanette Erdmann, Prof. Dr.Heribert Schunkert

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Erdmann | Jeanette | Prof. Dr. | Universität zu Lübeck, Institut für Integrative und Experimentelle Genomik | 3, 4 | SNP-vermittelte (Dys)Regulation in der Atherosklerose (TP3), SNP-vermittelte (Dys)Regulation in der Atherosklerose (TP4) |
| Dichgans | Martin | Prof. Dr. med. | Klinikum der Universität München, Institut für Schlaganfall- und Demenzforschung | 5 | Proteomweite Analysen zur Identifikation von funktionellen Einzelnukleotid Polymorphismen (SNPs) und assoziierten Schlüsselmolekülen bei arterieller Gefäßwandschädigung |
| Mann | Matthias | Prof. Dr. | Max-Planck-Institut für Biochemie, Department of Proteomics and Signal Transduction | 5 | Proteomweite Analysen zur Identifikation von funktionellen Einzelnukleotid Polymorphismen (SNPs) und assoziierten Schlüsselmolekülen bei arterieller Gefäßwandschädigung |
| Kuhn | Klaus | Prof. Dr. | Klinikum rechts der Isar der TU München, Institut für Medizinische Statistik und Epidemiologie | 6 | Datenintegration und Harmonisierung, Translation der Ergebnisse |
| Krüger | Bernd | Prof. Dr. | Universität Heidelberg, Universitätsmedizin Mannheim, V. Medizinische Klinik | 6 | Datenintegration und Harmonisierung, Translation der Ergebnisse |
| Schunkert | Heribert | Prof. Dr. | Deutsches Herzzentrum München, Klinik für Herz- und Kreislauferkrankungen | 7 | Organisations- und Koordinationsstelle |
| Schunkert | Heribert | Prof. Dr. | Deutsches Herzzentrum München, Klinik für Herz- und Kreislauferkrankungen | 5, 6, 7 | Proteomweite Analysen zur Identifikation von funktionellen Einzelnukleotid Polymorphismen (SNPs) und assoziierten Schlüsselmolekülen bei arterieller Gefäßwandschädigung (TP5), Datenintegration und Harmonisierung, Translation der Ergebnisse (TP6), Organisations- und Koordinationsstelle (TP7) |

## e:Kid

Systems medicine approach to personalized immunosuppressive treatment at early stage after Kidney Transplantation

Coordinator: Prof. Dr. Nina Babel

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Babel | Nina | Prof. Dr. | Charité - Universitätsmedizin Berlin | TP Charité | |
| Seitz | Harald | Dr. | Fraunhofer Institute for Cell Therapy and Immunology | TP IBMT | |

## e:Kid

Systems medicine approach to personalized immunosuppressive treatment at early stage after Kidney Transplantation

Coordinator: Prof. Dr. Nina Babel

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Baron | Udo | Dr. | Epiontis GmbH | TP Epiontis | |
| Schuchhardt | Johannes | Dr. | MicroDiscovery GmbH | TP Micro Discovery | |
| Hugo | Christian | Prof. Dr. | TU Dresden | TP TU Dresden | |
| Or-Guil | Michal | Dr. | Humboldt-Universität zu Berlin | TP HU Berlin | |

## IntegraMent

Integrated Understanding of Causes and Mechanisms in Mental Disorders

Coordinator: Prof. Dr. Markus Nöthen

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Nöthen | Markus | Prof. Dr. med | Universitätsklinikum Bonn | TP 1a | Data integration and systems modeling in mental disorders |
| Lange | Christoph | Prof. Dr. | Uni Bonn, Genomische Mathematik | TP 1b | Data integration and systems modeling in mental disorders |
| Mattheisen | Manuel | Prof. Dr.med | Department of Biomedicine | TP 1c | Data integration and systems modeling in mental disorders |
| Müller-Myhsok | Bertram | Prof. Dr.med | Max Planck Institut für Psychiatrie | TP 1d | Data integration and systems modeling in mental disorders |
| Theis | Fabian | Prof. Dr. | Helmholtz Zentrum, München | TP 1e | Data integration and systems modeling in mental disorders |
| Binder | Elisabeth | Dr.Dr. med. univ. | Max Planck Institut für Psychiatrie | TP 2a | Central patient resource and bridging between genotype and phenotype |
| Rietschel | Marcella | Prof. Dr. med | Zentral Institut für Seelische Gesundheit | TP 2b | Central patient resource and bridging between genotype and phenotype |
| Rujescu | Dan | Prof. Dr. med | Universität Halle | TP 2c | Central patient resource and bridging between genotype and phenotype |
| Fischer | André | Prof. Dr. rer. nat. | Georg-August-Universität Göttingen | TP 2d | Central patient resource and bridging between genotype and phenotype |
| Schulze | Thomas | Prof. Dr. med | Ludwig-Maximilians-Universität München | TP 2d | Central patient resource and bridging between genotype and phenotype |
| Nöthen | Markus | Prof. Dr. med | Universitätsklinikum Bonn | TP 3 | Large-scale molecular genetic studies |
| Cichon | Sven | Prof. Dr. rer. nat. | Universität Basel | | Large-scale molecular genetic studies |
| Schumacher | Johannes | PD Dr. med | Universitätsklinikum Bonn | | Large-scale molecular genetic studies |
| Meyer-Lindenberg | Andreas | Prof. Dr. med | Zentral Institut für Seelische Gesundheit | TP 4a | Transdiagnostic neurocognitive biomarkers for the major psychoses |

| **IntegraMent**<br>Integrated Understanding of Causes and Mechanisms in Mental Disorders<br>Coordinator: Prof. Dr. Markus Nöthen | | | | | |
|---|---|---|---|---|---|
| **Coordinator of subproject** | | | | **Subproject** | |
| Name | Firstname | Title | Institution | Nr | Title |
| Heinz | Andreas | Prof. Dr. med | Charité-Universitätsmedizin Berlin | | Transdiagnostic neurocognitive biomarkers for the major psychoses |
| Walter | Henrik | Prof. Dr.med Dr. phil. | Charité-Universitätsmedizin Berlin | TP 4b | Transdiagnostic neurocognitive biomarkers for the major psychoses |
| Grabe | Hans Jörgen | Prof. Dr.med Dr. phil. | Universität Greifswald | TP 5a | Impact of genetic risk factors for major psychiatric disease on mental and somatic pathology and resilience in the general population |
| Rietschel | Marcella | Prof. Dr.med Dr. phil. | Zentral Institut für Seelische Gesundheit | TP 5b | Impact of genetic risk factors for major psychiatric disease on mental and somatic pathology and resilience in the general population |
| Schulze | Thomas | Prof. Dr.med Dr. phil. | Ludwig-Maximilians-Universität München | TP 5c | Impact of genetic risk factors for major psychiatric disease on mental and somatic pathology and resilience in the general population |
| Fischer | André | Prof. Dr. rer. nat. | Georg-August-Universität Göttingen | TP 6a | Epigenetics and transcriptome plasticity in psychiatric disease |
| Giese | Armin | Prof. Dr. med | LMU Munich | TP 6b | Epigenetics and transcriptome plasticity in psychiatric disease |
| Falkai | Peter | Prof. Dr. med | LMU Munich | | Epigenetics and transcriptome plasticity in psychiatric disease |
| Wurst | Wolfgang | Prof. Dr. rer. nat. | Helmholtz Zentrum München | TP 7 | Identification of disease mechanisms for major psychiatric disorders using genetic mouse models |
| Deussing | Jan | Dr. rer. nat. | Max Planck Institut für Psychiatrie, | TP 7 | Identification of disease mechanisms for major psychiatric disorders using genetic mouse models |
| Wanker | Erich E. | Prof. Dr.-Ing. | Max-Delbrück-Centrum für Molekular Medizin(MDC) | TP 8 | Interactome networks and perturbed cellular functions in schizophrenia and bipolar disorder |
| Nöthen | Markus | Prof. Dr. med | Universitätsklinikum Bonn | TP 9 | Human iPS ell-based neuronal cultures for modeling neuropsychiatric disease |
| Brüstle | Oliver | Prof. Dr. med | Universität Bonn und Hertie-Stiftung | TP 9 | Human iPS ell-based neuronal cultures for modeling neuropsychiatric disease |
| Durstewitz | Daniel | Dr. rer. nat. | Zentral Institut für Seelische Gesundheit | TP 10 | Neurodynamic analysis of psychiatric disease mechanisms using computational network models |
| Nöthen | Markus | Prof. Dr. med | Universitätsklinikum Bonn | TP 11 | Project management and graduate training |

## Multiscale HCC

Systems Biology Supports Multiscale Analysis of Imaging, Omics and Clinical Data to Improve Diagnosis and Therapy of HCC

Coordinator: Prof. Dr. Bernd Pichler

| **Coordinator of subproject** | | | | **Subproject** | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Kohlbacher | Oliver | Professor | Center for Bioinformatics, Quantitative Biology Center, and Dept. of Computer Science, University of Tübingen | 3 | Data Management and Multiscale Computational Modeling |
| Reuss | Matthias | Prof.Dr.-Ing.Dr.h.c. | Stuttgart Research Center Systems Biology | 1,3 | Implementierung und Validierung von Anti-Angiogenese-Therapie-Modellen |
| Perfahl | Holger | Dr.rer.nat. | Stuttgart Research Center Systems Biology | 1,3 | Implementierung und Validierung von Anti-Angiogenese-Therapie-Modellen |
| Witteler-Neul | Beate | | Stuttgart Research Center Systems Biology | 1,3 | Implementierung und Validierung von Anti-Angiogenese-Therapie-Modellen |
| Daum | Volker | Dr.-Ing. | Chimaera GmbH | 4 | Bildanalyse und Auswertung für die Entwicklung von prädiktiven und prognostischen Modellen für die HCC Diagnose und Therapieantwort |
| Hahn | Dieter | Dr.-Ing. | Chimaera GmbH | 4 | Bildanalyse und Auswertung für die Entwicklung von prädiktiven und prognostischen Modellen für die HCC Diagnose und Therapieantwort |
| Pichler | Bernd | Professor | Abteilung für Präklinische Bildgebung und Radiopharmazie, Universität Tübingen | 1,2,5,6 | Diagnose und Therapie des hepatozellulären Karzinoms (HCC, Lebertumor) unter Einbeziehung von Omics-Methoden (Metabolom und Proteom als molekulare Parameter des Tumors), der Bildgebung und Methoden der Systemmodellierung, sowie das Management des Konsortiums |
| Schmid | Andreas | Dr. hum. sci. | Abteilung für Präklinische Bildgebung und Radiopharmazie, Universität Tübingen | 1,2,5,6 | Diagnose und Therapie des hepatozellulären Karzinoms (HCC, Lebertumor) unter Einbeziehung von Omics-Methoden (Metabolom und Proteom als molekulare Parameter des Tumors), der Bildgebung und Methoden der Systemmodellierung, sowie das Management des Konsortiums |
| Bezrukov | Ilja | | Abteilung für Präklinische Bildgebung und Radiopharmazie, Universität Tübingen | 1,2,5,6 | Diagnose und Therapie des hepatozellulären Karzinoms (HCC, Lebertumor) unter Einbeziehung von Omics-Methoden (Metabolom und Proteom als molekulare Parameter des Tumors), der Bildgebung und Methoden der Systemmodellierung, sowie das Management des Konsortiums |

## Multiscale HCC

Systems Biology Supports Multiscale Analysis of Imaging, Omics and Clinical Data to Improve Diagnosis and Therapy of HCC

Coordinator: Prof. Dr. Bernd Pichler

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Horger | Marius | Professor | Abteilung Radiologische Diagnostik, Universitätsklinikum Tübingen | 1,2,5,6 | Diagnose und Therapie des hepatozellulären Karzinoms (HCC, Lebertumor) unter Einbeziehung von Omics-Methoden (Metabolom und Proteom als molekulare Parameter des Tumors), der Bildgebung und Methoden der Systemmodellierung, sowie das Management des Konsortiums |
| Malek | Nisar | Professor | Abteilung Innere Medizin 1, Universitätsklinikum Tübingen | 1,2,5,6 | Diagnose und Therapie des hepatozellulären Karzinoms (HCC, Lebertumor) unter Einbeziehung von Omics-Methoden (Metabolom und Proteom als molekulare Parameter des Tumors), der Bildgebung und Methoden der Systemmodellierung, sowie das Management des Konsortiums |
| Zender | Lars | Professor | Abteilung Innere Medizin 1, Universitätsklinikum Tübingen | 1,2,5,6 | Diagnose und Therapie des hepatozellulären Karzinoms (HCC, Lebertumor) unter Einbeziehung von Omics-Methoden (Metabolom und Proteom als molekulare Parameter des Tumors), der Bildgebung und Methoden der Systemmodellierung, sowie das Management des Konsortiums |
| Bitzer | Michael | Professor | Abteilung Innere Medizin 1, Universitätsklinikum Tübingen | 1,2,5,6 | Diagnose und Therapie des hepatozellulären Karzinoms (HCC, Lebertumor) unter Einbeziehung von Omics-Methoden (Metabolom und Proteom als molekulare Parameter des Tumors), der Bildgebung und Methoden der Systemmodellierung, sowie das Management des Konsortiums |

## PANC-STRAT

Coordinator: Prof. Dr. Roland Eils

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Eils | Roland | Prof. Dr. | DKFZ Heidelberg | SP2 / SP4 / SP7 | Data Generation and Integrated Data Analysis / Dynamic Systems Biology Models / Integrated Data Management |
| Schlesner | Matthias | Dr. | DKFZ Heidelberg | SP2 | Data Generation and Integrated Data Analysis |
| Bauer | Tobias | Dr. | DKFZ Heidelberg | SP4 | Dynamic Systems Biology Models |

**PANC-STRAT**

An integrative approach towards personalized treatment of pancreatic cancer

Coordinator: Prof. Dr. Roland Eils

| **Coordinator of subproject** | | | | **Subproject** | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Lawerenz | Christian | | DKFZ Heidelberg | SP7 | Integrated Data Management |
| Trumpp | Andreas | Prof. Dr. | HI-STEM - Heidelberg Institute for Stem Cell Technology and Experimental Medicine gGmbH | SP3 / SP5 | Establishment of patient derived xenograft-models and personalized TIC cultures / Preclinical Translation |
| Sprick | Martin | Dr. | HI-STEM - Heidelberg Institute for Stem Cell Technology and Experimental Medicine gGmbH | SP3 / SP5 | Establishment of patient derived xenograft-models and personalized TIC cultures / Preclinical Translation |
| Werner | Jens | Prof. | Chirurgische Klinik München | | kein TP Leiter |
| Hackert | Thilo | Prof. Dr. | Ruprecht-Karls-Universität Heidelberg - Medizinische Fakultät und Universitätsklinikum Heidelberg - Chirurgische Klinik - Klinik für Allgemein-, Viszeral- und Transplantationschirurgie | SP1 / SP6 | Clinical Sample Collection, Preparation and Histological Evaluation / Clinical Translation of Results |
| Giese | Nathalia | Dr. | Ruprecht-Karls-Universität Heidelberg - Medizinische Fakultät und Universitätsklinikum Heidelberg - Chirurgische Klinik - Klinik für Allgemein-, Viszeral- und Transplantationschirurgie | SP1 / SP6 | Clinical Sample Collection, Preparation and Histological Evaluation / Clinical Translation of Results |
| Weichert | Wilko | Prof. Dr. | Ruprecht-Karls-Universität Heidelberg - Medizinische Fakultät und Universitätsklinikum Heidelberg - Pathologisches Institut | SP1 / SP6 | Clinical Sample Collection, Preparation and Histological Evaluation / Clinical Translation of Results |
| Springfeld | Christoph | Dr. | Ruprecht-Karls-Universität Heidelberg - Medizinische Fakultät und Universitätsklinikum Heidelberg - NCT Heidelberg - Medizinische Onkologie | SP1 / SP6 | Clinical Sample Collection, Preparation and Histological Evaluation / Clinical Translation of Results |
| Jäger | Dirk | Prof. Dr. | Ruprecht-Karls-Universität Heidelberg - Medizinische Fakultät und Universitätsklinikum Heidelberg - NCT Heidelberg - Medizinische Onkologie | SP1 / SP6 | Clinical Sample Collection, Preparation and Histological Evaluation / Clinical Translation of Results |

**SMOOSE**

Systems-level analysis of modulators of oncogenic signaling

Coordinator: Prof. Dr. Roman Thomas

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Bosco | Graziella | Dr. | UKK, Abt. Translationale Genomik | SP0 | Coordinating Office |
| Fischer | Matthias | Prof. Dr. | UKK, Kinderklinik | SP1a | Genomic characterization and modeling of tumor progression |
| Schulte | Johannes | Prof. Dr. | Uniklinik Essen | SP1b | Genomic characterization and modeling of tumor progression |
| Peifer | Martin | Dr. | UKK, Abt. Translationale Genomik | SP2 | Systems-level modeling of cancer genome evolution |
| Berg | Johannes | Prof. Dr. | UzK, Institut für Theoretische Physik | SP3 | Systems-level modeling of mutationally activatedsignaling networks and response to therapy |
| Lang | Urlich | Prof. Dr. Ing. | Rechenzentrum der Universität zu Köln | SP4 | Data handling, optimization of analysis workflows and applications |
| Thomas | Roman | Prof. Dr. | UKK, Abt. Translationale Genomik | SP5 | Identification, validation and exploitation of modulators |
| Reinhardt | Christian | Prof. Dr. | UKK, Innere Medizin I | SP6 | Modulation of oncogenic signaling through complex tumor/stroma interactions |
| Büttner | Reinhard | Prof. Dr. | UKK; Institut für Pathologie | SP7 | Modulation of oncogenic signaling through epigenetic writers of the histone code |
| Rauh | Daniel | Prof. Dr. | TU Dortmund, Chemische Biologie | SP8 | Chemical Biology of multi-pathway inhibition |
| Wolf | Jürgen | Prof. Dr. | UKK, Innere Medizin I, CIO | SP9a | Translational Research platform for rapid transfer of preclinical findings into personalized treatment approaches |
| Wolf | Jürgen | Prof. Dr. | UKK, Innere Medizin I, CIO | SP9b | Clinical Trial |

**SYSIMIT**

Mining the spatial patterns of adaptive immune responses to persisting tissue antigens to exploit the full predictive potential of protocol biopsies in transplantation and cancer research

Coordinator: Prof. Dr. Friedrich Feuerhake

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Meyer-Hermann | Michael | Prof. Dr. | Helmholtz-Zentrum | 1 | Mathematisches Modell der Entstehung ektopischer Lymphfollikel im Kontext von Nierentransplantationen |
| Schmidt | Günter | Dr. | Definiens AG | 2 | Bild- und Datenanalyse von räumlichen Immunzellmustern zur Entwicklung von neuen prognostischen Gewebemarkern |

**SYSIMIT**

Mining the spatial patterns of adaptive immune responses to persisting tissue antigens to exploit the full predictive potential of protocol biopsies in transplantation and cancer research

Coordinator: Prof. Dr. Friedrich Feuerhake

| **Coordinator of subproject** | | | | **Subproject** | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Hatzikirou | Haralampos | Dr. | Technische Universität Dresden | 3 | Mathematisches Modell der Interaktion zwischen T- und Epithelzellen in der lymphozytären Lobulitis bei erblichem Brustkrebs |
| Feuerhake | Friedrich | Prof. Dr. | Medizinische Hochschule Hannover | 4 | Prognostischer Wert der entzündlichen Reaktion auf erblichen Brustkrebs mit Fokus auf lymphozytäre Lobulitis |

**SysINFLAME**

A Systems Approach to Chronic Inflammatory Disease

Coordinator: Prof. Dr. Philip Rosenstiel, Prof. Dr. Stefan Schreiber

| **Coordinator of subproject** | | | | **Subproject** | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Schreiber | Stefan | Prof. Dr. | Klinik für Innere Medizin I, Institut für Klinische Molekularbiologie | AP | Administrative Project |
| Weidinger | Stephan | Prof. Dr. | Klinik für Dermatologie, Venerologie und Allergologie | CP1 | Monogenic and Oligenic Traits |
| August | Dietrich | - | Universitätsklinikum Freiburg, Center for Chronic Immunodeficiency | CP1 | Monogenic and Oligenic Traits |
| Rodriguez | Elke | Dr. | UKSH, Klinik für Dermatologie, Venerologie und Allergologie | CP1 | Monogenic and Oligenic Traits |
| Baurecht | Hansjörg | Dr. | UKSH, Klinik für Dermatologie, Venerologie und Allergologie | CP1 | Monogenic and Oligenic Traits |
| Grimbacher | Bodo | Prof. Dr. | Universitätsklinikum Freiburg | CP1 | Monogenic and Oligenic Traits |
| Kabesch | Michael | Prof. Dr. | Universität Regensburg | CP1 | Monogenic and Oligenic Traits |
| Lieb | Wolfgang | Prof. Dr. | Institut für Epidemiologie | CP2 | Kindred Cohorts |
| Franke | Andre | Prof. Dr. | Institut für Klinische Molekularbiologie | CP3 | Host Genetics meets Microbiome |
| Heinsen | Femke | Dr. | UKSH, IKMB | CP3 | Host Genetics meets Microbiome |
| Baines | John | Prof. Dr. | UKSH, Institut für Experimentelle Medizin | CP3 | Host Genetics meets Microbiome |
| Rosenstiel | Philip | Prof. Dr. | Institut für Klinische Molekularbiologie | CP4 | Epigenome /Transcriptome Dynamics |
| Häsler | Rob | Dr. | UKSH, IKMB | CP4 | Epigenome /Transcriptome Dynamics |
| Schreiber | Stefan | Prof. Dr. | Klinik für Innere Medizin I, Institut für Klinische Molekularbiologie | CP5 | Drug Response |

| **SysINFLAME**<br>A Systems Approach to Chronic Inflammatory Disease<br>Coordinator: Prof. Dr. Philip Rosenstiel, Prof. Dr. Stefan Schreiber | | | | | |
|---|---|---|---|---|---|
| **Coordinator of subproject** | | | | **Subproject** | |
| Name | Firstname | Title | Institution | Nr | Title |
| Radbruch | Andreas | Prof. Dr. | Deutsches Rheuma-Forschungszentrum (DRFZ) | CP6 | Immune Cell Dynamics |
| Löhnhardt | Benjamin | | Universitätsmedizin Göttingen, Institut für Medizinische Informatik | CP6 | Immune Cell Dynamics |
| Bauer | Christian | | Universitätsmedizin Göttingen, Institut für Medizinische Informatik | CP6 | Immune Cell Dynamics |
| Baum | Benjamin | | Universitätsmedizin Göttingen, Institut für Medizinische Informatik | CP6 | Immune Cell Dynamics |
| Laudes | Matthias | Prof. Dr. | Klinik für Innere Medizin I | CP7 | Redefinition of Phenotypes |
| Schulte | Dominik | | UKHS, Klinik für Innere Medizin I | CP7 | Redefinition of Phenotypes |
| Ellinghaus | Eva | Dr. | Institut für Klinische Molekularbiologie | CP8 | Comorbidities |
| Willenborg | Christina | | UKSH, Institut für Integrative und Experimentelle Genomik | CP8 | Comorbidities |
| Ellinghaus | David | | UKSH, IKMB | CP8 | Comorbidities |
| Krawczak | Michael | Prof. Dr. | Institut für Medizinische Informatik und Statistik | CP9 | Analysis and Systems Biology Dialog |
| Hütt | Marc | Prof. Dr. | Jacobs Universität Bremen | CP9 | Analysis and Systems Biology Dialog |
| Claussen | Jens Christian | PD Dr. | Jacobs University | CP9 | Analysis and Systems Biology Dialog |
| Fretter | Christoph | | Jacobs University | CP9 | Analysis and Systems Biology Dialog |
| Wolf | Andreas | | UKSH, Institut für Medizinische Informatik und Statistik | CP9 | Analysis and Systems Biology Dialog |
| Franke | Andre | Prof. Dr. | Institut für Klinische Molekularbiologie | CP10 | Data Management System |
| Sax | Ulrich | Prof. Dr. | Universitätsmedizin Göttingen | CP10 | Data Management System |
| Radbruch | Andreas | | Deutsches Rheuma-Forschungszentrum (DRFZ) | CP10 | Data Management System |
| Hemmrich-Stanisak | Georg | | UKSH, IKMB | CP10 | Data Management System |

**SysMed-Alcoholism**

Alcohol Addiction: A Systems-Oriented Approach

Coordinator: Prof. Dr. Rainer Spanagel

| **Coordinator of subproject** | | | | **Subproject** | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Spanagel | Rainer | Prof. Dr. | Institute of Psychopharmacology,Central Institute of Mental Health | SP1 | Coordination of the Consortium |
| Nöthen | Markus | Prof. Dr. | Universty of Bonn, Siegmund-Freud-Str. 25, 53127 Bonn | SP2 | Central Resource I: Genomics and Epigenomics |
| Rietschel | Marcella | Prof. Dr. | Department of Genetic Epidemiology,Central Institute of Mental Health | | Central Resource I: Genomics and Epigenomics |
| Hansson | Anita | Dr. | Institute of Psychopharmacology,Central Institute of Mental Health | SP3 | Central Resource II: Transcriptomics platform |
| Sommer | Wolfgang H. | PD Dr. | Institute of Psychopharmacology,Central Institute of Mental Health | | Central Resource II: Transcriptomics platform |
| Schloss | Patrick | Prof. Dr. | Central Institute of Mental Health | | Central Resource II: Transcriptomics platform |
| Schumann | Gunter | Prof. Dr. | Chair in Biological Psychiatry, MRC-SGDP Centre, Institute of Psychiatry, King's College | SP4 | Central Resource III: IMAGEN |
| Matthäus | Franziska | Dr. | BIOMS/IWR, University of Heidelberg, Im Neuenheimer Feld 267 | SP5 | Central Resource IV: Animal model of alcohol addiction |
| Vengeliene | Valentina | Dr. | Institute of Psychopharmacology,Central Institute of Mental Health | | Central Resource IV: Animal model of alcohol addiction |
| Obermeyer | Klaus | Prof. Dr. | Neural Information Processing Group, Fakultät IV,Technische Universität Berlin, MAR 5-6 | SP6 | Mathematical Modeling I: Convergent data analysis and statistics |
| Heinz | Andreas | Prof. Dr. | Department of Psychiatry, Charité – Universitätsmedizin,Berlin, Campus Charité Mitte | | Mathematical Modeling I: Convergent data analysis and statistics |
| Durstewitz | Daniel | Prof. Dr. | Central Institute of Mental Health | SP7 | Mathematical Modeling II: Local neurodynamics and treatment predictions |

| **SysMed-Alcoholism**<br>Alcohol Addiction: A Systems-Oriented Approach<br>Coordinator: Prof. Dr. Rainer Spanagel | | | | | |
|---|---|---|---|---|---|
| **Coordinator of subproject** | | | | **Subproject** | |
| Name | Firstname | Title | Institution | Nr | Title |
| Noori | Hamid | PD Dr. | Bernstein Center Heidelberg/Mannheim, Central Institute for Mental Health | SP8 | Mathematical Modeling III: Global neurotransmitter dynamics and target predictions |
| Scholz | Henrike | Prof. Dr. | Behavioral Neurogenetics" Zoologisches Institut,Biozentrum, Universität zu Köln | SP9 | Functional Validation I: Gene and molecular analysis |
| Wurst | Wolfgang | Prof. Dr. | Institute of Developmental Genetics, Helmholtz Zentrum Munich | | Functional Validation I: Gene and molecular analysis |
| Heinz | Andreas | Prof. Dr. | Department of Psychiatry, Charité – Universitätsmedizin,Berlin, Campus Charité Mitte | SP10 | Functional Validation II: Neuroimaging x genetics |
| Walter | Henrik | Prof. Dr. | Department of Psychiatry, Charité – Universitätsmedizin,Berlin, Campus Charité Mitte | | Functional Validation II: Neuroimaging x genetics |
| Kiefer | Falk | Prof. Dr. | Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health (CIMH) | | Functional Validation II: Neuroimaging x genetics |
| Köhr | Georg | PD Dr. | Central Institute of Mental Health,Medical Faculty Mannheim/ Heidelberg University | SP11 | Functional Validation III: Functional local network activity and neurotransmitter release |
| Spanagel | Rainer | Prof. Dr. | Institute of Psychopharmacology,Central Institute of Mental Health | | Functional Validation III: Functional local network activity and neurotransmitter release |
| Zimmermann | Ulrich | PD Dr. | Dept. of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus | SP12 | Platform for experimental human studies |
| Smolka | Michael | Prof. Dr. | Dept. of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus | | Platform for experimental human studies |

**SYSMED-NB**

Systems Medicine for Neuroblastoma

Coordinator: Prof. Dr. Angelika Eggert

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Eggert | Angelika | Prof. Dr. | Charité - Universitätsmedizin Berlin | SP C und SP A4 | |
| Westermann | Frank | PD Dr. | Deutsches Krebsforschungszentrum (DKFZ) | SPA1, SPA3, SPB1 und SPB4 | |
| Schramm | Alexander | PD Dr. | University Hospital Essen | SP A2 und SP B3 | |
| Rahmann | Sven | Prof. Dr. | TU Dortmund | | |
| Fischer | Matthias | Prof. Dr. | Universität zu Köln | SP A1 und SP B2 | |
| Schulte | Johannes Hubertus | Prof. Dr. | Universität Duisburg-Essen | SP A2 | |
| Selbach | Matthias | Prof. Dr. | Max-Delbrück-Centrum für Molekulare Medizin (MDC) | SP A3 und SP B3 | |
| Eilers | Martin | Prof. Dr. | Julius-Maximilians-Universität Würzburg | SP A5 | |

**Sys-Stomach**

Identification of predictive response and resistance factors to targeted therapy in gastric cancer using a systems medicine approach

Coordinator: Prof. Dr. Birgit Luber, Dr. Dieter Maier

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | Firstname | Title | Institution | Nr | Title |
| Luber | Birgit | Prof. Dr. | Technische Universität München | TP 1 | Systematische molekulare und phänotypische Charakterisierung von Magenkarzinom-Zelllinien |
| Maier | Dieter | Dr. | Biomax Informatics AG | TP 2 | Wissensmanagement und Biomarkeridentifizierung |
| Theis | Fabian | Prof. Dr. Dr. | Helmholtz Zentrum München | TP 3 | Multilevel Analyse von Magenkarzinomdaten |
| Meyer-Hermann | Michael | Prof. Dr. | Helmholtz-Zentrum für Infektionsforschung | TP 4 | Agenten-basierte Modelle von Tumoren zur Definition von adjuvanten Therapieansätzen |
| Walch | Axel | Prof. Dr. | Helmholtz Zentrum München, Institut für Pathologie | TP 5 | In-situ Proteomanalyse des Magenkarzinoms |
| Lordick | Florian | Prof. Dr. | Universitäres Krebszentrum Leipzig (UCCL) | TP 6 | Klinische Validierung von vorhergesagten Response- und Resistenzfaktoren zielgerichteter Therapien beim Magenkarzinom |

e:Med
SYSTEMS MEDICINE

# List of e:Med Demonstrators for an Individualized Medicine

## HaematoOPT

Model-based optimisation and individualisation of treatment strategies in haematology

Coordinator: Prof. Dr. Ingo Röder

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Loeffler | Markus | Prof. Dr. | University Leipzig | | |
| Hochhaus | Andreas | Prof. Dr. | Jena University Hospital | | |
| Rudolph | Karl Lenhard | Prof. Dr. | Leibniz-Institut für Altersforschung | | |
| von Gersdorff | Gero | Dr. | Uniklinik Köln | | |

## HER2Low

Mathematische Modellierung der Wirkungsweise von gegen HER2, EGFR und ERBB3 gerichteten therapeutischen Antikörpern zur Personalisierung der Brustkrebstherapie

Coordinator: Dr. Ulrike Korf

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Timmer | Jens | Prof. Dr. | Universität Freiburg | SP 3 | ODE-based modeling of drug response in HER2-low breast cancer |
| Beißbarth | Tim | Prof. Dr. | Universitätsmedizin Göttingen | SP 4 | Pathway-activation profiling of clinical samples for biomarker discovery |
| Schneeweiss | Andreas | Prof. Dr. | Heidelberg University Hospital | | |
| Vetter | Martina | Dr. | University Hospital Halle | | |
| Korf | Ulrike | Dr. | DKFZ Heidelberg | | |

## MAPTor-NET

MAPTor-NET: MAPK-mTOR network model driven individualized therapies of pancreatic neuro-endocrine tumors (pNETs)

Coordinator: Prof. Dr. Christine Sers

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Sers | Christine | Prof. Dr. | Charité Berlin | SP-TL | Analysis of therapy response in patients and cell lines with specific mutation profiles |
| Thedieck | Kathrin | Prof. Dr. | Universität Oldenburg | SP 1 | mTOR Signaling analysis and proteomic approaches |
| Blüthgen | Nils | Prof. Dr. | Charité Berlin | SP 2 | Mathematical large-scale modelling of signaling pathways in pancreatic neuroendocrine tumors (pNET) |
| Pavel | Marianne | Prof. Dr. med. | Charité Berlin | SP 3 | Patient recruitment, biomaterial sampling and clinical data management |
| Detjen | Katharina | Dr. | Charité Berlin | SP 4 | Development and functional characterization of pNET model systems |
| Leser | Ulf | Prof. Dr. | HU, Berlin | SP 5 | Data analysis, management and integration |

## Melanoma sensitivity

Predicting individual sensitivity of malignant melanoma to combination therapies by statistical and network modeling on innovative 3D organotypic screening models

Coordinator: Dr. Dagmar Kulms

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Kulms | Dagmar | PD Dr. | Universitätsklinikum Dresden | TP1 | Validating the predictive SYSACT model under organotypic 3D conditions using TRAIL/IZI1551-derivatives and trametinib/dabrafenib |
| Sauter | Thomas | Prof. Dr.-Ing. | Université du Luxembourg | TP 2 | Extending the SYSACT model by Boolean model based network analysis incorporating TRAIL and MEK signaling networks |
| Meier | Friedegund | Prof. Dr. med. | Universitätsklinikum Dresden | TP 3 | Translation and clinical validation of biomarkers predicted by SYSACT |
| Kontermann | Roland | Prof. Dr. | Universität Stuttgart | TP 4 | Generation and validation of therapeutically relevant, novel TRAIL-fusion proteins |
| Pfizenmaier | Klaus | Prof. Dr. | Universität Stuttgart | TP 4 | Generation and validation of therapeutically relevant, novel TRAIL-fusion proteins |

## MITO-PD

Mitochondrial endophenotypes of PD

Coordinator: Prof. Dr. Thomas Gasser

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Kohlbacher | Oliver | Prof. Dr. | Universität Tübingen | TP 2 | Data management and integration |
| Balling | Rudi | Prof. Dr. | Université du Luxembourg | TP 3 | Computational modeling of mitochondrial dysfunction |
| Heutink | Peter | Prof. Dr. | DZNE | TP 4 | Validation in cellular models |
| Jain | Shushant | Dr. | DZNE | TP 4 | Validation in cellular models |
| Gasser | Thomas | Prof. Dr. | HIH & DZNE | TP 4 | Validation in cellular models |
| Krüger | Rejko | Prof. Dr. | HIH & DZNE | TP 4 | Validation in cellular models |
| Klein | Christine | Prof. Dr. | Universität Lübeck | TP 4 | Validation in cellular models |
| Ueffing | Marius | Prof. Dr. | Universität Tübingen | TP 4 | Validation in cellular models |
| Gloeckner | Christian Johannes | Dr. | Universität Tübingen | TP 4 | Validation in cellular models |
| Wurst | Wolfgang | Prof. Dr. | HelmholtzZentrum München | TP 5 | Mitochondrial endophenotypes of Parkinson's Disease |
| Ueffing | Marius | Prof. Dr. | Universität Tübingen | TP 5 | Mitochondrial endophenotypes of Parkinson's Disease |

## MMML-Demonstrators

Molecular Mechanisms in Malignant Lymphomas - Demonstrators of Personalized Medicine

Coordinator: Prof. Dr. Rainer Spang

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Klapper | Wolfram | Prof. Dr. | CAU Kiel | SP 1 | NanoString Platforms |
| Ott | German | Prof. | Robert-Bosch-Krankenhaus | SP 2 | Validation of prognostically relevant stroma signatures in the prospectively randomized RICOVER60 and MegaCHOEP phase II and phase III trials |
| Trümper | Lorenz | Prof. Dr. med. | Universitätsmedizin Göttingen | SP 2 | Validation of prognostically relevant stroma signatures in the prospectively randomized RICOVER60 and MegaCHOEP phase II and phase III trials |
| Loeffler | Markus | Prof. Dr. | Universität Leipzig | SP 3 | Toponomic Models of the architectures of lymphomas |
| Engelmann | Julia | Dr. | Universität Regensburg | SP 4 | Identification of molecular targets for immunotherapy of lymphoma using causal modeling |
| Beissbarth | Tim | Prof. Dr. | Universität Göttingen | SP 5 | Simulation of combination therapies |
| Lottaz | Lottaz | Dr. | Universität Regensburg | SP 6 | LYMMML, a web-portal for interactive access to the MMML data repositories |

## SMART

Systems Medicine of Heart Failure

Coordinator: Prof. Dr. med. Titus Kühne

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Schapranow | Matthieu-P. | Dr. | Hasso-Plattner-Institut | SP 2 | Real-Time Analysis of Genome Data using In-Memory Database Technology |
| Falcke | Martin | Dr. | MDC für Molekulare Medizin | SP 4 | Cell physiology modelling and proteomics |
| Dittmar | Gunnar | Dr. | MDC für Molekulare Medizin | SP 4 | Cell physiology modelling and proteomics |
| Kühne | Titus | Prof. Dr. med. | DHZB/Charité | SP 5 | Image based modelling (DHZB/Charite) |
| Thomas | Wendl | Dr. | Bayer Technology Services GmbH | SP 6 | Mechanistic multiscale models |

**SYS-GLIO**

Systems-based predictors for the biological and clinical behavior of gliomas

Coordinator: Prof. Dr. Peter Lichter

| **Coordinator of subproject** | | | | **Subproject** | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Eils | Roland | Prof. Dr. | DKFZ & Universität Heidelberg | SP 1A | Integrative analysis of genome-wide data sets |
| Schlesner | Matthias | Dr. | DKFZ | SP 1A | Integrative analysis of genome-wide data sets |
| Höfer | Thomas | Prof. Dr. | DKFZ | SP 1B | Mathematical modeling of glioma growth |
| Lichter | Peter | Prof. Dr. | DKFZ | SP 2A | Assessment of crucial pathways in validation cohort |
| Loeffler | Markus | Prof. Dr. | Universität Leipzig | SP 2B | Assessment of crucial pathways in validation cohort |
| Reifenberger | Guido | Prof. Dr. | Universität Düsseldorf | SP 2B | Assessment of crucial pathways in validation cohort |
| von Deimling | Andreas | Prof. Dr. | Universität Heidelberg | SP 2B | Assessment of crucial pathways in validation cohort |
| Weller | Michael | Prof. Dr. | UniversitätsSpital Zürich | SP 2B | Assessment of crucial pathways in validation cohort |
| Pfister | Stefan | Prof. Dr. | DKFZ | SP 3A | In vivo validation in glioma mouse models |
| Liu | Hai-Kun | Dr. | DKFZ | SP 3A | In vivo validation in glioma mouse models |
| Gronych | Jan | Dr. | DKFZ | SP 3A | In vivo validation in glioma mouse models |
| Reifenberger | Guido | Prof. Dr. | Universität Düsseldorf | SP 3B | Experimental modeling of glioma progression and therapy resistance |
| Knobbe-Thomsen | Christiane | Dr. | Universität Düsseldorf | SP 3B | Experimental modeling of glioma progression and therapy resistance |
| Weller | Michael | Prof. Dr. | UniversitätsSpital Zürich | SP 3B | Experimental modeling of glioma progression and therapy resistance |
| Lamszus | Katrin | Prof. Dr. | Universitätsklinikum Hamburg-Eppendorf | SP 3C | Metabolic adaptations in glioma progression and therapy resistance |
| Radlwimmer | Bernhard | Dr. | DKFZ | SP 3C | Metabolic adaptations in glioma progression and therapy resistance |
| Weller | Michael | Prof. Dr. | UniversitätsSpital Zürich | SP 4 | Development of a clinical trial protocol |
| von Deimling | Andreas | Prof. Dr. | Universität Heidelberg | SP 4 | Development of a clinical trial protocol |
| Loeffler | Markus | Prof. Dr. | Universität Leipzig | SP 4 | Development of a clinical trial protocol |
| Lichter | Peter | Prof. Dr. | DKFZ | SP 4 | Development of a clinical trial protocol |
| Reifenberger | Guido | Prof. Dr. | Universität Düsseldorf | SP 4 | Development of a clinical trial protocol |
| Pfister | Stefan | Prof. Dr. | DKFZ | SP 4 | Development of a clinical trial protocol |

e:Med
SYSTEMS MEDICINE

# List of e:Med
# Junior Research Alliances

## DeCaRe

Systems biology analysis of cardiac regeneration to improve healing after myocardial infarction

Coordinator: Prof. Dr. David Hassel

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Hassel | David | Prof. Dr. | University Hospital Heidelberg | SP 1 | Identification and characterization of novel miRNA-controlled signalling circuitries during zebrafish heart regeneration |
| Leuschner | Florian | Dr. Dr. | University Hospital Heidelberg | SP 2 | The role of inflammation in cardiac regeneration in Zebrafish |
| Hassel | David | Prof. Dr. | University Hospital Heidelberg | | Die Rolle von miRNAs und miRNA regulierter Signalwege sowie inflammatorischer Prozesse bei der Herzregeneration |
| Börries | Melanie | Dr. Dr. | DKFZ Heidelberg | | In silico Multiomics Modellierung von Signalwegen bei der Herzregeneration |
| Dobreva | Gergana | Prof. Dr. | MPI für Herz- und Lungenforschung | | Epigenetische Regulation der kardialen Regeneration |

## GlioPATH

Comparison of central metabolic routes and signaling pathways in IDH mutant and wildtype gliomas

Coordinator: Dr. Christiane Opitz

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Schäuble | Sascha | Dr. | University Jena | SP 1 | Modeling of metabolic changes in human IDHmut and IDHwt gliomas. |
| Opitz | Christiane | Dr. | DKFZ Heidelberg | SP 2 | Experimental analysis of Trp and NAD metabolism in human gliomas and integration of the experimental and modeling results of the consortium with clinical data |
| Trump | Saskia | Dr. | Helmholtz-Zentrum für Umweltforschung, Leipzig | SP 3 | The role of AHR activation on metabolism and methylation in IDHmut and IDHwt human gliomas. |
| Thedieck | Kathrin | Prof. Dr. | University Oldenburg | SP 4 | mTOR interactions with metabolic networks in malignant glioma: an integrative experimental-computational approach |

## MILES

Multi-disciplinary identification of lineage-specific signaling dependencies in Cancer

Coordinator: Dr. Martin Sos

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Clement-Ziza | Mathieu | Dr. | Zentrum für Molekulare Medizin Köln | SP 1 | Transcription factor activity variation across cancer lineages |
| Sos | Martin | Dr. | University Hospital of Cologne | | |
| Peifer | Martin | Dr. | University of Cologne | | |
| Seeger-Nukpezah | Tamina | Dr. | University Hospital of Cologne | | |
| Sunyaev | Ali | Prof. Dr. | University of Cologne | SP 5 | Verarbeitung sensibler medizinischer Informationen in Cloud-Computing-Umgebungen bei gleichzeitiger Wahrung von Informsationssicherheit und -privatheit |

## mitOmics

Identification of molecular causes of mitochondrial defects by personalised omics approaches

Coordinator: Dr. Julien Gagneur

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Perocchi | Fabiana | Dr. | Helmholtz Zentrum München | | Identifizierung von kausalen Krankheitsgenen und Signalwegen durch systematische und personalisierte genetische Interaktionskartierung |
| Haack | Tobias | Dr. | Helmholtz Zentrum München | | Definition der genetischen Architektur durch Genomsequenzierung und Transkriptionsanalyse |
| Gagneur | Julien | Dr. | Gene center of the LMU Muenchen | SP 3 | Integrative analysis to infer mutations and pathways causal for the disease |

## PsychoSys

The role of dopamine in sensory inference and delusions: a systems medicine approach to psychosis

Coordinator: Dr. Simon Jacob

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Schmack | Katharina | Dr. med. | Charité Berlin | SP 1 | The neurobiology of delusions: linking perceptual inference and dopamine |
| Jacob | Simon | Dr. | TU München | SP 2 | The role of human dopamine neurons in perceptual inference |
| Sigurdsson | Torfi | Dr. | Goethe-Universität Frankfurt am Main | SP 3 | Dopaminergic signaling and sensory prediction in genetic mouse models of schizophrenia |
| Schneider | Gaby | Prof. Dr. | Goethe-Universität Frankfurt am Main | SP 4 | A generalized stochastic framework for linking perceptual and physiological processes in dysfunctional sensory predictions |

## SUPR-G

Systems biology of the Unfolded Protein Response in Glioma

Coordinator: Dr. Björn Tews

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Medenbach | Jan | Dr | Universität Regensburg | SP 1 | Towards a transcriptome-wide and integrated vision of the translation branch of the unfolded protein response in glioma |
| Ahrends | Robert | Dr. | ISAS Dortmund | SP 2 | A systems biology approach to determine the equilibrium of the unfolded protein response |
| Toedt | Grischa | Dr | EMBL Heidelberg | SP 3 | Systems biology of the Unfolded Protein Response in Glioma (SUPR-G) |
| Knobbe-Thomsen | Christiane | Dr. med. | Heinrich-Heine-Universität Düsseldorf | SP 4 | Towards understanding the UPR in infiltrating glioma cells |
| Tews | Björn | Dr. | DKFZ Heidelberg | SP 5 | Functional characterization of secreted proteins mediating glioma cell invasion |

## symATRIAL

Systems Medicine of Atrial Fibrillation

Coordinator: Prof. Dr. Tanja Zeller

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Schillert | Arne | Dr. | Universität zu Lübeck | SP 1 | Infrastructure of data management and data exchange |
| Schillert | Arne | Dr. | Universität zu Lübeck | SP 2 | Omics analyses and longitudinal gene expression analysis |
| Heinig | Matthias | Dr. | Helmholtz Zentrum München | SP 3 | Regulatory networks and computational systems biology |
| Zeller | Tanja | Prof. Dr. | | SP 4 | Molecular characterization of AF candidate genes and pathways and translation |
| Schnabel | Renate | PD Dr. | Universitäres Herzzentrum Hamburg | SP 5 | Genomic Epidemiology of Atrial Fibrillation |

## SYMBOL-HF

Systems Medicine to dissect the Biology of Heart Failure

Coordinator: Prof. Dr. Steffen Just

| Coordinator of subproject | | | | Subproject | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Just | Steffen | Prof. Dr. | Universitätsklinikum Ulm | SP 1 | Funktionelle Genomik im Zebrafisch zur Aufklärung molekularer Netzwerke der Herzinsuffizienz |
| Kestler | Hans | PD Dr. | University Ulm | | Modellanalyse der Herzinsuffizienz |
| Gramlich | Michael | Dr. | Universitätsklinikum Tübingen | SP 3 | Functional Genomics in Human Heart Failure |
| Frank | Derk | Dr. | Universitätsklinikum Schleswig-Holstein | | Funktionelle Genomik zu molekularen Netzwerken der Herzinsuffizienz im Zusammenhang mit mechanischem Zellstress |

**TIL-REP**

Dynamics of the tumor infiltrating lymphocyte repertoire in melanoma and pancreatic cancer

Coordinator: Dr. Isabel Poschke

| **Coordinator of subproject** | | | | **Subproject** | |
|---|---|---|---|---|---|
| Name | First Name | Title | Institution | Nr | Title |
| Diken | Mustafa | Dr. | TRON, Universitätsmedizin Mainz | SP 1 | TIL dynamics in a mouse model of melanoma |
| Floßdorf | Michael | Dr. | DKFZ Heidelberg | SP 2 | Data-based mathematical modeling of the anti-tumor T-cell response |
| Poschke | Isabel | Dr. | DKFZ Heidelberg | SP 3 | TIL repertoire in melanoma and pancreatic ductal adenocarcinoma |
| Hassel | Jessica | Dr. | Universitätsklinikum Heidelberg | SP 4 | Tumor-reactive T-cells and response to immune checkpoint blockers |
| Strobel | Oliver | PD Dr | Universitätsklinikum Heidelberg | SP 5 | TIL dynamics in pancreatic ductal adenocarcinom |

Space for notes

Space for notes

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