e:Med Meeting 2017 on Systems Medicine

November 21 - 23, 2017
Alte Mensa, University of Göttingen

e:Med
SYSTEMS MEDICINE

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Scientific Program Committee

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Prof. Dr. Markus Nöthen
Institute of Human Genetics, University Hospital Bonn

Prof. Dr. Karsten Rippe
German Cancer Research Center (DKFZ), BioQuant Heidelberg

Prof. Dr. Philip Rosenstiel
Institute of Clinical Molecular Biology (IKMB), CAU Kiel, UKSH

Prof. Dr. Tanja Zeller
University Medical Center Hamburg-Eppendorf, Hamburg

Welcome Remarks 2017

It is a great pleasure to cordially welcome you all on behalf of the e:Med Project Committee and the local organizers at the **4th e:Med Meeting 2017 on Systems Medicine** held November 21 – 23 at the bright and delightful **"Alte Mensa" in Göttingen**.

We are very much looking forward to a stimulating three-day conference program featuring **17 keynote lectures** by invited international speakers, **17 short talks** by e:Med experts, **22 poster flash talks, 4 company sessions** and a poster exhibition with more than **120 posters** reflecting the active e:Med community. The top three posters will be honored with the **e:Med 2017 Poster Award.** The conference opens with a **satellite workshop on technical innovations**, organized by the e:Med project group epigenetics & sequencing. A special highlight is the evening event "Karriere in der Systemmedizin" with **public talks for young investigators** and systems medicine "unplugged" by Uri Alon.

Outstanding experts in the interdisciplinary field of systems medicine will inspire us with presentations on state-of-the-art research and the latest developments from e:Med projects and beyond. The program covers important topics from **technologies** and **models in systems medicine** to **causes and courses of diseases** and concludes with the **translation into the clinics.** Sessions on **European systems medicine** as well as **systems medicine impulse talks** inform on international and overarching projects. Moreover, recent technological developments are on display in **company lectures** and the **industrial exhibition** of our sponsors. You are cordially invited to actively participate in meetings and presentations of all e:Med project groups. Take a look at the program to find the diverse activities throughout the conference and join the discussions with other experts in your field of interest.

The e:Med annual meeting would not be feasible without the help of our supporters: First and foremost we are very grateful to the *BMBF* for funding the e:Med program. In addition, the generous support of our company sponsors allows us to have the **get together** on Tuesday 21st and the **conference dinner** on Wednesday 22nd with live music at the historic restaurant Bullerjahn.

Take the opportunity to meet your e:Med colleagues and actively engage in the discussions on the many aspects of systems medicine in the unique atmosphere of the renowned university town Göttingen.

Professor Dr. Tanja Zeller Professor Dr. Karsten Rippe

Speakers of the e:Med project committee

Members of the e:Med Project Committee

Prof. Dr. Nina Babel, Charité Berlin

Prof. Dr. Friedrich Feuerhake, Hannover Medical School

Dr. Roberto Goya-Maldonado, Georg August University Göttingen

Prof. Dr. Steffen Just, University Hospital Ulm

Dr. Frank Kramer, Georg August University Göttingen

Prof. Dr. Dagmar Kulms, University Hospital Carl Gustav Carus, Dresden

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

Prof. Dr. Markus Löffler, Leipzig University

Prof. Dr. Markus Nöthen, University of Bonn

Prof. Dr. Ingo Röder, Technische Universität Dresden

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

Prof. Dr. Martin Sos, University Hospital of Cologne

Prof. Dr. Rainer Spang, Universität Regensburg

Prof. Dr. Roman Thomas, University of Cologne

Prof. Dr. Tanja Zeller, University Medical Center Hamburg-Eppendorf, Hamburg

Dr. Michael Ziller, Max Planck Institute of Psychiatry, München

Conference Management

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Prof. Dr. Ulrich Sax
Department of Medical Informatics
University Medical Center Goettingen
Georg-August-University Goettingen

Oral Presentations

The time slots for oral presentations are as follows - please prepare your presentation accordingly and strictly respect the time limits:

Keynote Speaker **25 min talk** + 5 min discussion

Short Talk **12 min talk** + 3 min discussion

Slide desk

Please **hand in your slides for presentation on an USB stick at the Slide Desk** in the lecture hall latest until the session before your presentation. A Windows **PC is available for Powerpoint presentations**. To ensure an efficient course of the sessions, we can allow the use of your own computer only in exceptional cases, e.g. if you need a special program to present a movie embedded in your presentation. All presentation files will be deleted after the conference.

Poster Presentations

Each poster has been **assigned an abstract number** listed in this book beginning page 111. Posters will be discussed in the poster exhibition as follows:

Poster Session I
Odd numbers
Tuesday, November 21, 05.00 – 06.30 pm

Poster Session II:
Even numbers
Wednesday, November 22, 05.30 – 07.00 pm

During this time, the presenting author is expected at the poster in order to present the data.

Please note:

- Posters may be **set-up** November 21, 2017, from 10.00 am to 1.30 pm.
- Poster pins/strips to fix your poster will be provided on tables at exhibition site.
- Posters may be removed at the end of the conference. Remaining posters can not be sent.

e:Med Poster Award 2017

All posters will be evaluated by the program committee panel and the top three posters will be awarded € 150 each. The ceremony is scheduled for Thursday, November 23, 2017 around 3:30 pm.

Award criteria:

- scientific quality and novelty
- concise statement of significance of research
- focused problems, innovative solutions
- succinct, clear, engaging presentation
- visual balance between text, figures and tables

Important
The Poster Award will only be allocated to participants who are present at the award ceremony or who have nominated a representative who will present their poster.

Internet Connection - WLAN Access

WLAN access is available during the conference via **eduroam.**
To alternatively use an open guest network, please please ask at the registration desk for WLAN Code.

Evening Networking Events

- **Get together with wine & snacks** at the venue on Tuesday, November 21.
- **Dinner at the restaurant Bullerjahn** on Wednesday, November 22 starting from 7:30 pm.
  The restaurant is located in the old townhall of Göttingen (Markt 9, http://www.bullerjahn.info). Enjoy the historic atmosphere of the vaulted cellar with nice food followed accompanied with electronic music by Maewen Forest (https://soundcloud.com/maewenmusic).
  Dinner is offered for free, drinks are asked to be paid by each participant. Please note that you need to be registered to join this event.

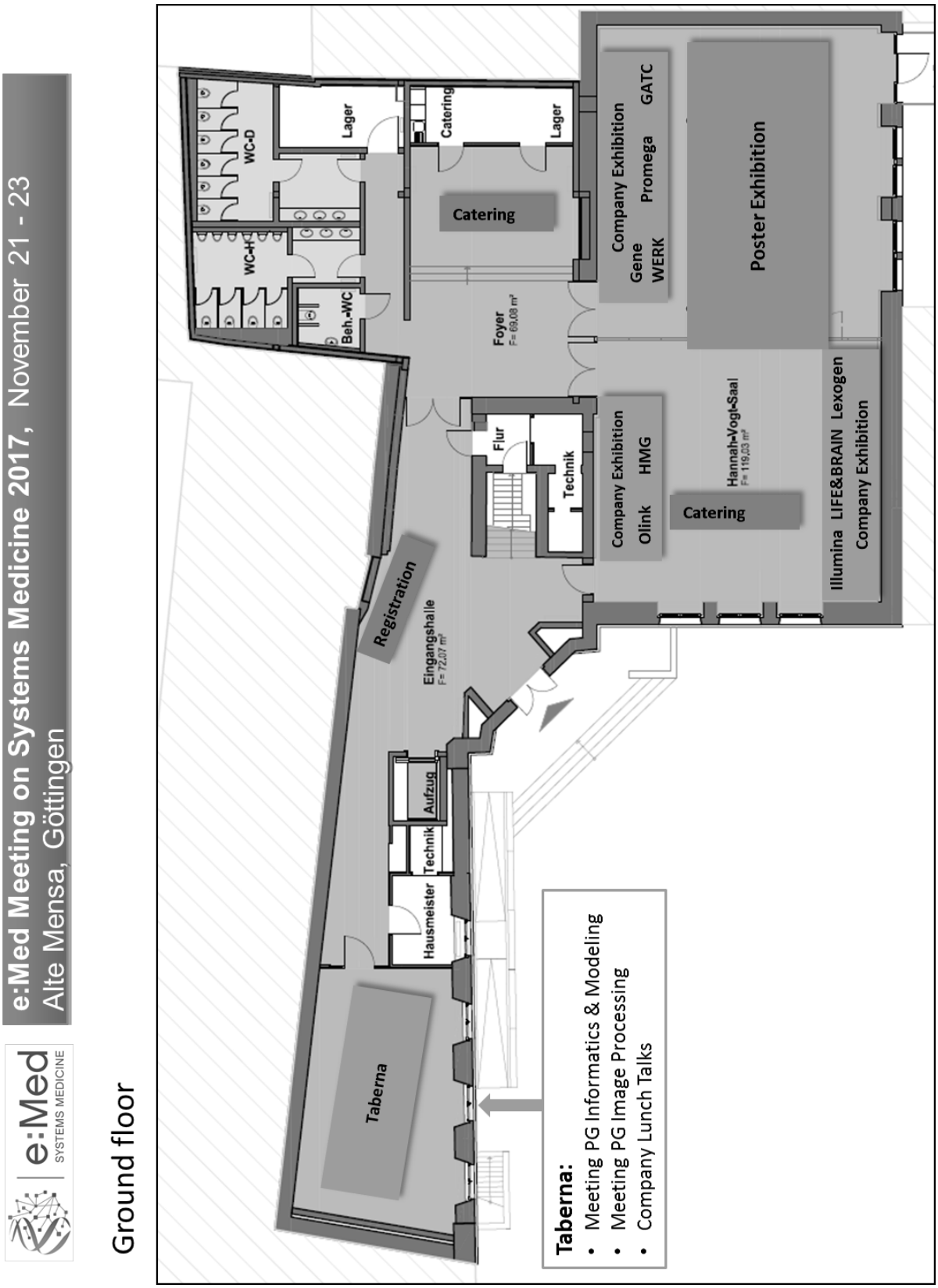
Cell Phones

Please turn off your cell phone during all sessions!

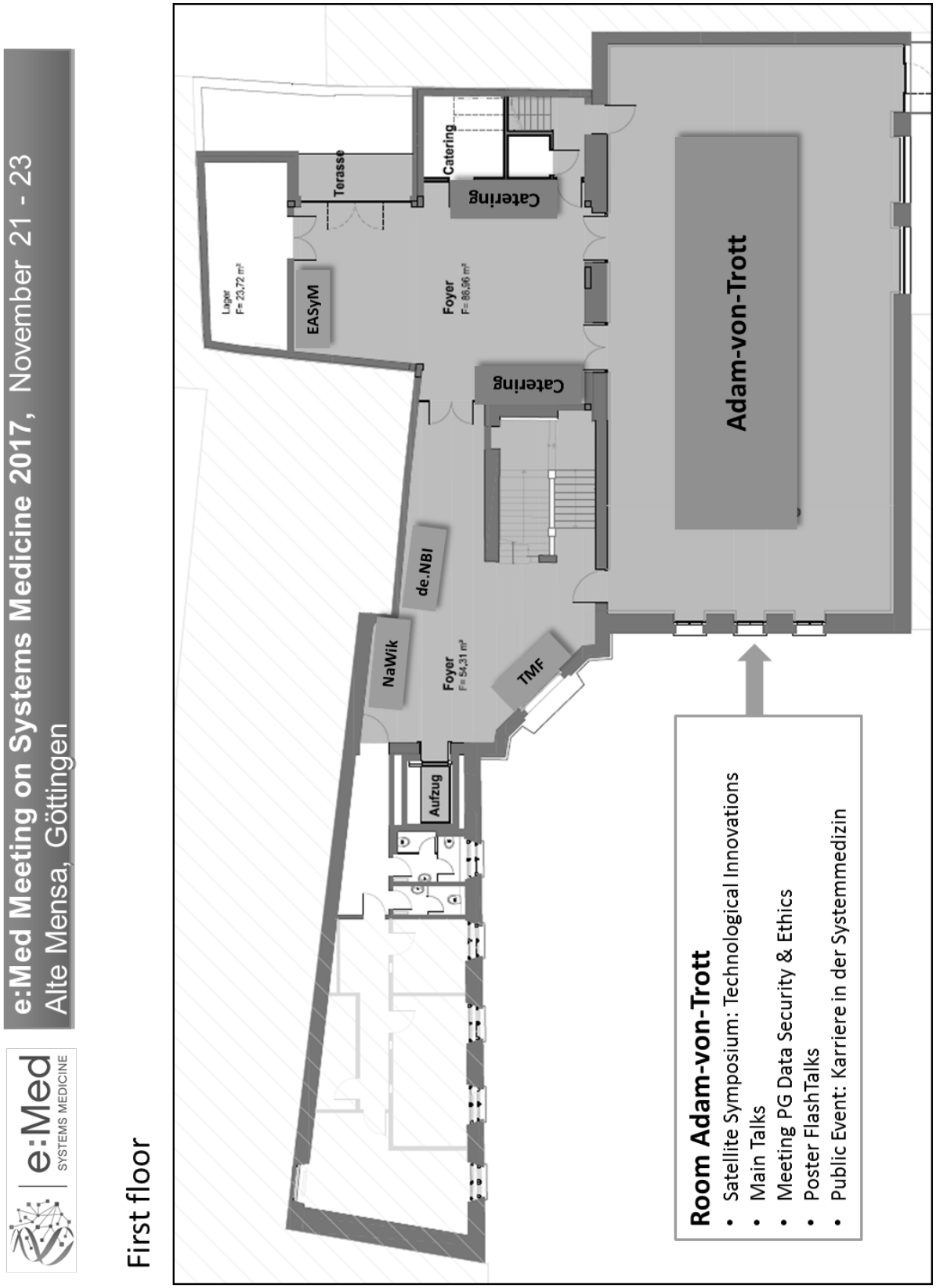
Photography

It is strictly forbidden to take pictures of any scientific data. We encourage participants to share their unpublished data, hence, do not photograph any posters or slides.

Venue: Ground floor



Venue: First floor



Organisation Program

Tuesday, November 21, 2017	
10:00 - 11:00 am	**Breakout Project Group: PG 1 Informatics & Modelling** **Chair PG 1: Matthias Ganzinger**
11:00 - 01:00 am	**Satellite Symposium: Technological Innovations** Organized by Project group Epigenetics & Sequencing Chair: Philip Rosenstiel, Friedrich Feuerhake, Karsten Rippe
11:00 - 11:30 am	**Angela Vasaturo, INSERM, Paris** *Unraveling the tumor microenvironment architecture by multispectral imaging*
11:30 - 12:00 pm	**Philipp Mallm, DKFZ Heidelberg** *Follow response to treatment by single-cell sequencing*
12:00 - 12:30 pm	**Andreas Schlitzer, University of Bonn** *Unravelling Cellular heterogeneity - A single cell biology approach*
12:30 - 01:00 pm	**Stefan Günther, MPI Bad Nauenheim** *High resolution single cell analysis in complex adult tissues*
01:00 - 01:45 pm	**Registration & Welcome Supper**
01:45 - 02:00 pm	**Welcome Address** **Tanja Zeller,** Spokesperson e:Med Project Committee **Blanche Schwappach,** UMG/Uni Göttingen **Johannes Mohr**, Bundesministerium für Bildung und Forschung
02:00 - 02:45 pm	**Uri Alon, Weizmann Institute, Israel** Visionary talk: *Design principles of circuits for tissue homeostasis*
02:45 - 04:00 pm	**Technologies in Systems Medicine** Chair: Philip Rosenstiel, Frank Kramer
02:45 - 03:15 pm	**Benno Schwikowski, Institut Pasteur** Keynote: *LEAN analysis biological network hot spots in the age of Big Data*
03:15 - 03:30 pm	**Wolfram Gronwald, University of Regensburg** *Metabolomic Changes in Lymphoma in Response to Stromal Stimuli*
03:30 - 03:45 pm	**Katharina Nekolla, Definiens AG, Munich** *Spatial organization of B cells and T cells predicts loss of renal transplant function*
03:45 - 04:00 pm	**Chris Lawerenz, DKFZ Heidelberg** *Introducing the de.NBI Cloud – the novel compute and storage infrastructure for life sciences*
04:00 - 04:30 pm	**Coffee Break**
04:30 - 06:30 pm	**Poster Session I (odd numbers)** Chair: Ingo Röder
04:30 - 05:00 pm	**Poster Flash Talks (11 talks à 3 min)**
05:00 - 06:30 pm	**Poster Exhibition**
06:30- 07:45 pm	**Karriere in der Systemmedizin: Public session for young investigators** (English/Deutsch) Moderation: Friedrich Feuerhake **Roberto Goya-Maldonado** *Wie lebt der Arzt die Systemmedizin?* **Frank Kramer** *Als Informatiker in der Systemmedizin* **Antje Walz** *Karriere in der Industrie* **Markus Nöthen** *Perspektive des Senior Scientists* **Uri Alon** *Systems Medicine "unplugged*"
07:45 - 10:00 pm	**Get Together with Wine & Snacks - Networking at Venue**

Top Thema

Wednesday, November 22, 2017	
08:30 - 09:00 am	**Morning Coffee**
09:00 - 10:30 am	**Systems Medicine in European Context** Chair: Peter Lichter, Karsten Rippe
09:00 - 09:30 am	**Philip Rosenstiel, University of Kiel** *SYSCID – A systems medicine approach to chronic inflammatory*
09:30 - 10:00 am	**Bernd Pichler, University of Tübingen** *German imaging science in European context*
10:00 - 10:30 am	**Markus Löffler, University of Leipzig** *Medical Informatics Initiative and Systems Medicine Initiative*
10:30 - 11:00 am	**Coffee Break**
11:00 - 12:30 pm	**Systems Medicine of Diseases** Chair: Roberto Goya-Maldonado, Dagmar Kulms
11:00 - 11:30 am	**Conor Liston, Weill Cornell Medical College, NYC** Keynote: *Frontostriatal mechanisms of anhedonia in novel neurophysiological subtypes of depression*
11:30 - 11:45 am	**Julia Krause, University Medical Center Hamburg-Eppendorf, DZHK** *Metabolomics in Translational Medicine – A Link between Acylcarnitines and Atrial Fibrillation*
11:45 - 12:00 pm	**Nima Abedpour, University of Cologne** *Reconstruction of tumor evolution from massively parallel sequencing data*
12:00 - 12:15 pm	**Elisa Espinet, HI-STEM & DKFZ** *Transcriptomic landscape of Pancreatic Cancer and normal Epithelial and Stromal cells directly isolated from human samples reveals common and cell-type specific deregulated nodes*
12:15 - 12:30 pm	**Vicente Yépez, TU Munich** *Multi-omics analysis methods for the genetic diagnosis of rare diseases*
12:30 - 02:30 pm	**Lunch Break**
01:00 - 02:10 pm	**Company Lunch Talks**
01:00 - 01:30 pm	**Martin Lundberg,** Olink Proteomics: *A precision proteomics solution for targeted human protein biomarker discovery*
01:40 - 02:10 pm	**Ingolf Cascorbi,** UKSH for HMG Systems Engineering *HMG Systems Engineering: Clinical Implementation of Pharmacogenetics*

Wednesday, November 22, 2017 continued	
02:30 - 04:00 pm	**Modelling in systems medicine** Chair: Friedrich Feuerhake, Markus Löffler
02:30 - 03:00 pm	**Antje Walz, Roche Basel** Keynote: *From Ideas to Medicine – with Modelling and Simulation*
03:00 - 03:15 pm	**Dagmar Kulms,TU Dresden** *Predicting sensitivity of malignant melanoma to combination therapies by network modeling*
03:15 - 03:30 pm	**Peter-Martin Bruch, University Hospital Heidelberg** *A drug - cytokine interaction map for lympho-proliferative disorders*
03:30 - 03:45 pm	**Kathrin Thedieck, University Medical Center Groningen & University Oldenburg** *Computational modelling of amino acid signaling to kinase networks*
03:45- 04:00 pm	**Verena Körber, DKFZ Heidelberg** *Clonal evolution in adult glioblastoma*
04:00 - 04:30 pm	**Coffee Break**
04:30 - 05:00 pm	**Datenschutzgrundverordnung** Organized by Project group Data security & Ethics Chair: Christoph Schickhardt
04:30 - 05:00 pm	**Boris Reibach, University of Oldenburg** *Der neue EU-Datenschutz: Folgen für die Forschung*
05:00 - 07:00 pm	**Poster Session II (even numbers)** Chair: Tanja Zeller
05:00 - 05:30 pm	**Poster Flash Talks (11 talks à 3 min)**
05:30 - 07:00 pm	**Poster Exhibition**
06:45 - 07:30 pm	**Breakout Project Groups**
	PG 2: Data security & Ethics **Room Adam-von-Trott** **Chair PG 2: Christoph Schickhardt**
	PG 3: Image processing **Taberna** **Chair PG 3: Bernd Pichler**
07:30 - 11:00 pm	**e:Med Dinner & Party Göttingen Restaurant Bullerjahn**

Thursday, November 23, 2017	
08:30 - 09:00 am	**Morning Coffee**
09:00 - 10:30 am	**Systems Medicine Impulse Talks** Chair: Ingo Röder, Michael Ziller
09:00 - 09:30 am	**Oliver Kohlbacher, University of Tuebingen (iD:Sem)** *Closing the translational gap – integrating of high-throughput data for personalized cancer treatments into clinical processes*
09:30 - 10:00 am	**Peter Jansen, AMC Amsterdam (LiSyM)** *Progressive fibrosis as driving force behind liver cirrhosis, liver failure and hepatocellular carcinoma*
10:00 - 10:30 am	**Alfred Pühler, University of Bielefeld (de.NBI)** *The German Network for Bioinformatics Infrastructure de.NBI Helps to Handle Big Data in Life Sciences*
10:30 - 11:00 am	**Coffee Break**
11:00 - 12:30 pm	**Sytems Medicine Approaches in Clinics I** Chair: Markus Nöthen, Nina Babel
11:00 - 11:30 am	**Erwin Böttinger, HPI & University of Potsdam** Keynote: *Translational approaches for progressive diseases*
11:30 - 11:45 am	**Sylvane Desrivières, King's College London, United Kingdom** *Updates on the ENIGMA-Epigenetics Working Group*
11:45 - 12:00 pm	**Ateequr Rehman, Christian-Albrechts-University Kiel** *Anti-TNFα restores disrupted metabolic interaction of the intestinal microbiome in IBD*
12:00 - 12:15 pm	**Nina Babel, Charité – Universitätsmedizin Berlin** *Multi-omics based strategy to predict graft function and personalize immunosuppressive therapy in kidney transplantation*
12:15 - 02:15 pm	**Lunch Break**
12:50 - 01:55 pm	**Company Lunch Talks**
12:50 - 01:20 pm	**Karsten Rippe, DKFZ and Matthias Prucha, Illumina** *Illumina: Experiences from the 2017 e:Med Summer School How advancements in Next Generation Sequencing support Functional Genomics Research*
01:25 - 01:55 pm	**Lukas Paul, Lexogen GmbH** *Lexogen: Gene Expression Profiling of Blood Samples: QuantSeq 3' mRNA-Seq Library Preparation with Globin Reduction*
02:15 - 03:30 pm	**Sytems Medicine Approaches in Clinics II** Chair: Tanja Zeller, Roman Thomas
02:15- 02:45 pm	**Julia Stingl, University of Bonn** Keynote: *Pharmacogenomics: from translational research to next generation benefit-risk evaluation*
02:45 - 03:00 pm	**Mathew Divine, University of Tübingen** *Integrating multi-omics and multi-modality medical imaging to assess hepatocellular carcinoma patient outcome under Sorafenib treatment: A progress report of the Multiscale HCC project*
03:00 - 03:15 pm	**Ingo Roeder, TU Dresden** *"Systems hematology" – Opportunities, benefits, and limitations*
03:15 - 03:30 pm	**Tim Beißbarth, University Medical Center Göttingen** *How to report somatic variants in molecular tumor boards*
03:30 - 03:45 pm	**e:Med Poster Award Ceremony and Closing Remarks** Moderation: Karsten Rippe, Roberto Goya-Maldonado
	Karsten Rippe, Spokesperson e:Med Project Committee
03:45 - 04:15 pm	**Coffee & Snacks**

Speakers

Tue Nov 21 Satellite Symposium on technological innovations

11:00 - 11:30 am **Unraveling the tumor microenvironment architecture by multispectral imaging**
Angela Vasaturo

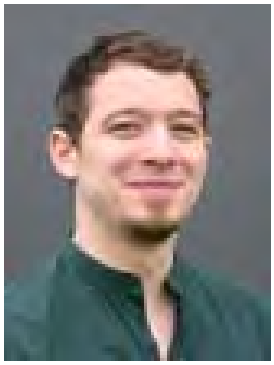
Dr. Angela Vasaturo is a Senior Researcher in the field of Tumor Immunology in the Integrative Cancer Immunology at the Cordeliers Research Center in Paris, France.
Dr. Vasaturo was trained as a Medical Biotechnologist and pursued a Ph.D. degree in Chemical Engineering (both at University of Naples "Federico II", Naples, Italy). She's been working as Post-doctoral researcher at the NCMLS in the years 2010-2015, being the recipient of an EMBO short-term fellowship, amongst others. She joined Dr. Jerome Galon's Laboratory of Integrative Cancer Immunology at the Cordeliers Research Center in 2015.
Dr Vasaturo has a sound knowledge on a broad range of in vivo and in vitro skills, and has a keen interest in microscopy and state-of-the-art imaging techniques, including Multispectral Imaging.
Dr. Vasaturo has published 16 papers in top-tier scientific journals, delivered seminars and tutorials internationally and carried out multiple collaborations in the field.

11:30 - 12:00 pm **Follow response to treatment by single-cell sequencing**
Jan-Philipp Mallm

Jan-Philipp Mallm performed his PhD work in the group of Karsten Rippe at the German Cancer Research Center (DKFZ, Heidelberg). Here he studied chromatin feedback on telomere maintenance in embryonic stem cells and on DNA repair in cancer initiating cells.
During his postdoc he exploited epigenetic deregulation in chronic lymphocytic leukemia (CLL) revealing a transcription factor network controlling the disease phenotype. Since 2015 he heads the Chromatin and RNA methods (CHARM) lab within the Heidelberg Center for Personalized Oncology (HIPO) establishing (single-cell) sequencing readouts for primary tumor samples.
In addition, in 2017 he started as a Team Leader for dissecting cellular heterogeneity in leukemic patients by single-cell sequencing approaches in the division of Karsten Rippe.

Tue Nov 21 Satellite Symposium on technological innovations

12:00 - 12:30 pm **Unravelling Cellular heterogeneity - A single cell biology approach**
Andreas Schlitzer



After his studies in Marburg and Manchester, Andreas Schlitzer did his PhD at the Technical University of Munich with a focus on dendritic cells. After his PhD he moved to the lab of Florent Ginhoux, Singapore Immunology Network, Singapore were he investigated how the functional polarization of myeloid cells is enforced using various single cell biology approaches, such as single cell transcriptomics, high dimensional flow cytometry and mass cytometry. Since 2016 he is an Emmy Noether Group leader at the Life & Medical Sciences Institute of the University of Bonn and employs an integrated single cell biology approach to identify the molecular mechanisms guarding myeloid cell differentiation and functional polarization during inflammation.

12:30 - 01:00 pm **High resolution single cell analysis in complex adult tissues**
Stefan Günther

Stefan Günther is currently the head of the next-generation core facility, Bioinformatics and Deep Sequencing Platform at the Max-Planck-Institute for Heart- and Lung Research in Bad Nauheim. He studied biology at the Martin-Luther University Halle-Wittenberg, where he received his Diploma in 2002. For his PhD, he joined the MPI for Heart-and Lung research. There he investigated muscle-specific transcription factors. From 2009 - 2013 he was a postdoctoral research fellow at the department of cardiac development and remodeling with Prof. Dr. Thomas Braun with focus on muscle stem cells. Dr. Günther is co-author of numerous publications in the area of nucleic acid research and single-cell sequencing.

Tue Nov 21 — Welcome Remarks

01:45 - 01:50 pm **Tanja Zeller, Speaker e:Med Project Comittee**

Professor Dr. Tanja Zeller is spokesperson of the e:Med project committee and professor for Genomics and Systems Biology at the University Heart Center Hamburg. She is head of the e:Med junior research alliance symAtrial. In her research, she investigates the molecular mechanisms of atrial fibrillation and additional cardiovascular diseases with the aim to identify genes and signaling pathways contributing to disease.

01:50 - 01:55 pm **Blanche Schwappach, UMG/Uni Göttingen**

Professor Dr. Blanche Schwappach is research dean of the University Medical Center Göttingen and head of the department of molecular biology. She received her PhD from the University Hamburg in 1996. After working as a scientist in San Franciso, Heidelberg and Manchester, she joined the University of Göttingen in 2010 where she became Professor and Director of the Department of Molecular Biology. Her research focus is membrane protein biogenesis in different physiological conditions.

01:55 - 02:00 pm **Johannes Mohr, BMBF**

Dr. Johannes Mohr is assistant head of division 614, Development of Methods and Structures in the Life Sciences, at the Federal Ministry of Education and Research (BMBF) since 2016. Dr. Mohr studied physics and received his PhD from the Technical University of Berlin.

Tue Nov 21 — Systems Medicine Visionary Talk

02:00 - 02:45 pm

Design principles of circuits for tissue homeostasis
Uri Alon

Born in Tel Aviv, Israel, Prof. Uri Alon earned his BSc in physics and mathematics, and his MSc in physics from the Hebrew University of Jerusalem (1989). He was awarded his PhD in physics from the Weizmann Institute of Science (1996), and was a postdoctoral fellow in experimental biology in the Departments of Physics and Molecular Biology at Princeton University (1997-1999), before taking a position at the Weizmann Institute in 1999. He is the incumbent of the Abisch-Frenkel Professorial Chair.

Prof. Alon works at the interface between physics and biology, and is one of the founders of the field of systems biology. Prof. Alon has made influential discoveries, chief among them that biological networks are made of repeating circuit patterns called network motifs. His team includes physicists and biologists working together to understand the principles of the molecular systems that guide the decisions of our bodies' cells. He is currently developing cocktails of drugs to combat cancer at low doses that avoid side effects, defining the design principles for hormone circuits and their susceptibility to aging and diseases such as type 2 diabetes, neurodegeneration and depression. He also studies principles of human behavior using concepts from theater and accurate physics measurements and mathematical models.

Prof. Alon received the 2014 Nakasone prize awarded by the Human Frontiers Science Project for a breakthrough in the life sciences for his work on network motifs and the Jacques Solvay Chair in Physics in 2017.

He was awarded the Michael Bruno Memorial Award in 2009 from the Yad Hanadiv Foundation. His previous prizes and honors include: the Moore Fellowship, California Institute of Technology (2000), EMBO Young Investigator Award (2001), Minerva Junior Research Group on Biological Computation (2003), Morris L. Levinson Award in Biology of the Weizmann Institute's Scientific Council (2003), IBM Faculty Award (2003), the Overton Prize of the International Society for Computational Biology (2004).

Prof. Alon is an enthusiastic father of three daughters, Gefen, Tamar, and Carmel. He acts and teaches in Playback Theatre, an improvisation theatre that aims to connect people by listening to real life stories told by audience members and enacting them on the spot.

Uri is an outspoken advocate of the importance of good human relationships in science, as seen on his 2013 TED talk.

02:45 - 03:15 pm

Keynote: LEAN analysis biological network hot spots in the age of Big Data
Benno Schwikowski

Dr. Schwikowski is a pioneer in the area of computational network and systems biology, and applications to biomedical problems. After training as a mathematician and computer scientist in Germany and the U.S., Dr. Schwikowski joined the Institute for Systems Biology in Seattle as one of its first group leaders. Besides creating algorithms around transcriptomics and proteomics, he established the 'guilt by association' principle to integrate molecular interaction data with protein function and transcriptomic data. His Cytoscape platform for the data-driven analysis of biological networks, is today one of the most widely used bioinformatics tools. Now at the Pasteur Institute in Paris, Dr. Schwikowski's group focuses on methods that enable data-driven strategies for disease stratification and biomarker discovery in immune-related and other complex diseases.

03:15 - 03:30 pm

Metabolomic Changes in Lymphoma in Response to Stromal Stimuli
Wolfram Gronwald

I was born and grew up in Hamburg in northern Germany. After completion of high school I studied chemistry at the Technical University of Braunschweig, Germany.
At that time I became fascinated by the possibilities that computational approaches together with experimental methods offer for the study of biological objects such as 3D protein structures and small organic molecules. Something I pursued from that time on through my whole career first as a Ph.D. student, as a post-doc at the University of Alberta in Canada and now with my own research group at the University of Regensburg in Germany.

03:30 - 03:45 pm

Spatial organization of B cells and T cells predicts loss of renal transplant function
Katharina Nekolla

Katharina Nekolla is a physicist by training who already focused on biomedical image and data analysis during her bachelor and master theses. She received her doctorate from the University of Munich on the distribution of nanoparticles in the tissue and their interaction with immune cells. Subsequently, she joined Definiens AG as a research scientist. At Definiens AG, the tissue phenomics methodology is applied to discover novel prognostic and predictive biomarkers mainly in the field of cancer immunotherapy. Katharina actively participates in several collaborative research projects - in the framework of SYSIMIT she investigates predictive biomarkers based on the spatial organization of immune cells in transplant kidney biopsies. The BMBF-funded consortium SYSIMIT aims at exploiting the full predictive potential of protocol biopsies in transplantation and cancer research by mining the spatial patterns of adaptive immune responses to persisting tissue antigens.

03:45 - 04:00 pm

Introducing the de.NBI Cloud – the novel compute and storage infrastructure for life sciences
Chris Lawerenz

Chris Lawerenz leads the Data Management and Genomics IT group in the division Theoretical Bioinformatics at DKFZ. His main interest is the project organization of IT projects in the context of large-scale scientific and biomedical data. His group provides data management and data processing for national and international collaborations in the field of basic and translational cancer research as well as for DKFZ internal needs. Some major collaborations are effecting the group activities, e.g. the three German projects within the International Cancer Genome Consortium (ICGC), the German Epigenom Programm (DEEP) and various sequencing projects in the context of systems medicine and personalized medicine. On the operational level, he coordinates The Heidelberg Center for Human Bioinformatics (HD-HuB). HD-HuB bundles bioinformatics expertise from three established research institutions in Heidelberg: German Cancer Research Center (DKFZ), European Molecular Biology Laboratory (EMBL) and Heidelberg University. Since 2016 he coordinates the Heidelberg de.NBI Cloud and the de.NBI Cloud federation.

Wed Nov 22 — Systems medicine in the European context

09:00 - 09:30 am

SYSCID – A systems medicine approach to chronic inflammatory diseases
Philip Rosenstiel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Uni Kiel

Philip Rosenstiel is head-member of the Institute of Clinical Molecular Biology at Kiel University and University Hospital Schleswig Holstein. He holds a professorship in Molecular and Evolutionary Medicine. He studied medicine in Kiel and Boston. He received his MD degree on the characterization of Angiotensin II as a neurotrophic factor in 2003. His main scientific interest is to contribute to an understanding of the complex interactions between human intestinal mucosa and the environment in health and disease. Emphasis is given to the translation of positional genetic signals in inflammatory bowel disease into distinct, functional molecular effects in underlying cellular pathways and networks. He also develops novel tools and techniques using large-scale sequencing and bioinformatics to understand regulatory events and cellular/bacterial response profiles in model systems of chronic inflammatory diseases. He serves as coordinator of several large-scale research initiatives in human diseases (e.g. BMBF SysINFLAME, H2020 SYSCID).

09:30 - 10:00 am

German imaging science in European context
Bernd Pichler

Prof. Dr. Bernd Pichler is director of the Werner Siemens Imaging Center and chair of the Department of Preclinical Imaging and Radiopharmacy, Clinic of Radiology, University of Tübingen, Germany. He earned his PhD in physics at the Department of Nuclear Medicine, Technical University of Munich, in 2002 and subsequently worked at the Department of Biomedical Engineering, University of California, Davis, USA. In 2005 Bernd Pichler became head of the Laboratory for Preclinical Imaging and Imaging Technology at the University of Tübingen. In December 2007, Dr. Pichler accepted the call of the University of Tübingen for a full (W3) professorship in “Preclinical Imaging and Imaging Technology”. In 2008 he became head of the Radiopharmacy and in 2011 both, the Laboratory for Preclinical Imaging of the Werner Siemens-Foundation and the Radiopharmacy joined, to become the Department of Preclinical Imaging and Radiopharmacy, with Prof. Pichler as director and chair of the department. His work includes multi-modality imaging in oncology, immunology and neurology as well as the development of new imaging technologies and innovative imaging probes.

Wed Nov 22 — Systems medicine in the European context

10:00 - 10:30 am

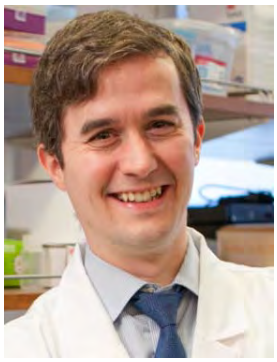
Medical Informatics Initiative and Systems Medicine Initiative
Markus Löffler

Dr. Markus Löffler is Professor and Director of the Institute of Medical Informatics, Statistics and Epidemiology in Leipzig. He is the acting director of the Center of Clinical Trials Leipzig, scientific director of the Interdisciplinary Center for Bioinformatics, as well as the director of the LIFE Research Center for Civilisation Diseases.
He is originally trained as a physicist and medical doctor and was promoted as a professor in medical documentation, statistics and biomathematics from the University of Cologne. In 1994 he became a full Professor and head of the Institute at the University of Leipzig. His research interests include clinical trials and cohort studies for molecular markers, bioinformatics, systems biology models as well as medical statistics and epidemiology. Dr. Löffler has an h-index of 87 and published numerous publications with far more than 30.000 citations.

Wed Nov 22 — Systems Medicine of Diseases

11:00 - 11:30 am

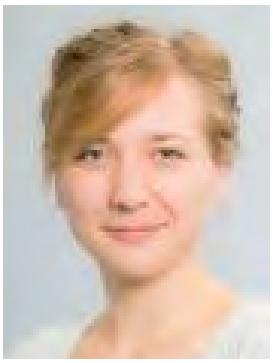
Keynote: Frontostriatal mechanisms of anhedonia in novel neurophysiological subtypes of depression
Conor Liston



Conor Liston is an Assistant Professor of Neuroscience and Psychiatry at the Feil Family Brand and Mine Research Institute and Department of Psychiatry at Weill Cornell Medicine. He studied Medicine and Neuroscience at Harvard and Weill Cornell Medical College and received his PhD from the Rockefeller University. After postdoctoral research at New York University and at Stanford, he became an Assistant Professor of Neuroscience at Weill Cornell in 2014. His research seeks to identify prefrontal circuit mechanisms supporting learning and memory and to understand how they are disrupted in stress-related psychiatric disorders, operating at the interface between systems neuroscience and biological psychiatry.

11:30 - 11:45 am

Metabolomics in Translational Medicine – A Link between Acylcarnitines and Atrial Fibrillation
Julia Krause



Julia Krause is a PhD student in the group of Molecular Cardiology, Genomics and Systems Biology at the University Heart Center Hamburg, Germany. She graduated in 2015 in Molecular Medicine at the Friedrich-Schiller-University Jena, Germany. Her PhD thesis is embedded in the multi-disciplinary e:Med symAtrial consortium and aims to identify and characterize atrial fibrillation-related genes, respective pathways and their functional assessment. Closely working together with clinicians, bioinformaticians and epidemiologists, multiple –omics data ranging from genomics, transcriptomics, miRNAs, to proteomics and metabolomics in atrial tissue and blood-based samples, are generated and bioinformatically integrated. The findings of these -omics analyses are investigated and the molecular role of identified candidates is further characterize by using different molecular experimental approaches and cell models.

11:45 - 12:00 pm

Reconstruction of tumor evolution from massively parallel sequencing data
Nima Abedpour

Nima is currently a postdoctoral researcher at department of translational genomics at the university of Cologne. He is considered as an interdisciplinary scientist working at the interface between Physics, Information Technology and Biology. In 2009, He received his PhD in physics in the field of complex systems at the Sharif University in Tehran. Throughout his physics education and a short postdoc after that, his work was mainly focused on statistical and computational physics. His curiosity about “the life” brought him toward biology research. In 2011, he was granted an EMBO Fellowship to study biological networks especially bacterial metabolic networks. From then on, he has been doing research in theoretical biology from different aspects. Currently he is focused on cancer genomics research. His research has benefited from machine learning approaches and statistical and mathematical modeling.

12:00 - 12:15 pm

Transcriptomic landscape of Pancreatic Cancer and normal Epithelial and Stromal cells directly isolated from human samples reveals common and cell-type specific deregulated nodes
Elisa Espinet

Elisa studied Chemistry at University of Valladolid, Spain. After this, she moved to the Laboratory of Eduard Batlle and Elena Sancho at the Institute for Research in Biomedicine (IRB) in Barcelona. There, as part of her PhD thesis, she uncovered the importance of TGFβ-activated cancer associated fibroblasts in the initiation of colorectal cancer metastasis and the association of stromal gene signatures with patient´s poor outcome.
After completing her PhD with honours, Elisa received an EMBO Fellowship to join the group of Andreas Trumpp at the German Cancer Research Center (DKFZ) in Heidelberg as postdoctoral researcher. Her main focus during the past years has been the generation of a comprehensive transcriptomic landscape of the cell-types present in human Pancreatic Ductal Adenocarcinoma (PDAC) for a better understanding of the complex molecular make up of this disease. Of big interest are inter- and intra-patient heterogeneity, especially in regards of tumor-stroma interactions.

12:15 - 12:30 pm

Multi-omics analysis methods for the genetic diagnosis of rare diseases
Vicente Yépez

Vicente Yépez was born in Quito, Ecuador. He graduated as Industrial Engineer during his bachelor studies in México. He gained professional experience working in different companies such as Novatech (Ecuador) and Tetra Pak and Kellogg's (Mexico). Then, he engaged in a masters program in Mathematical Modeling offered by the University of L'Aquila, Italy. He did his master's thesis in the "Numerical Modeling of the spread of populations". Currently, he is on his last year of a PhD in Bioinformatics, under Julien Gagneur's group in the Technical University of Munich (TUM), Germany and part of the Graduate School of Quantitative Biosciences Munich. His PhD thesis is based on statistical estimation of oxygen consumption rates and genetic diagnosis of rare diseases using multiomics data.

Wed Nov 22 — Modelling in Systems Medicine

02:30 - 03:00 pm

Keynote: From Ideas to Medicine – with Modelling and Simulation
Antje Walz

Antje Walz, Senior Principal Scientist, Translational Modelling & Simulation, Pharma Research and Early Development, Roche Innovation Center Basel, Switzerland.
Antje received her PhD in Biology from the University Konstanz, Germany in 2002. She brings 15 years of experience in drug discovery and development of small and large molecules. Since 2008, she works in the translational Modelling and Simulation group at Roche. Her main interest is to predict efficacy, biomarker and safety profiles in cancer patients based on nonclinical information. In her role as Pharmacokinetic/Pharmacodynamic (PK/PD) Franchise leader for oncology she develops M&S strategies and provides guidance to peers and project teams to select the most favorable compounds and optimal dose and dosing regimen in cancer patients with translational M&S.

03:00 - 03:15 pm

Predicting sensitivity of malignant melanoma to combination therapies by network modeling
Dagmar Kulms

Dr. Kulms studied Biology at the University of Gießen. During her PhD at the Medical University of Lübeck, she analysed the thermostablility of archebacterial proteins. Changing subjects she moved as a postdoc to the Laboratory of Cell Biology, Department of Dermatology, University of Münster, where she started investigating the adverse effects UVB radiation of human skin. She received the Venia Legendi for „Molecular and Cellular Biology“ in 2003. In 2004 she became an Assistant Professor and Group Leader of „Molecular and Cellular Biology“ at the Institute of Cell Biology and Immunology at the University of Stuttgart, and continued her word on skin cancer shifting the focus on melanoma. Here she also started first collaborations with Systems Biology groups. In 2012 she founded the research group of „Experimental Dermatology“ at the Department of Dermatology, Technical University of Dresden, and was assigned a Professor of Experimental Dermatology in 2015.

03:15 - 03:30 pm

A drug - cytokine interaction map for lympho-proliferative disorders
Peter-Martin Bruch

Peter-Martin Bruch started medical school in 2012. He has great interest in molecular medicine and hematology-oncology, aiming at a career as physician scientist in this medical field based on a combined clinical and scientific education. Previously he has worked in the field of oncology in multiple different settings, including the National Center for Tumor diseases. He received the Franziska Kolb foundation scholarship in May 2017, which allows him to interrupt his studies to conduct his MD thesis. His research focus is to understand the functional role of critical signaling pathways in lympho-proliferative diseases determining the biological basis for differential response to signals provided by the microenvironment. He has designed and currently conducts a high throughput drug-cytokine combinational perturbation screen in primary patient derived lymphoma and leukemia cells. His project is integrated in a close collaboration (SYMPATHY project) between the Heidelberg University Hospital (Sascha Dietrich), the DKFZ (Thorsten Zenz) and EMBL (Wolfgang Huber).

03:30 - 03:45 pm

Computational modelling of amino acid signaling to kinase networks
Kathrin Thedieck

Prof. Dr. Kathrin Thedieck joined the Universities of Oldenburg and Groningen in 2013 in the frame of the European Medical School (EMS). For more than 10 years she has been studying the kinase networks centered on phosphatidylinositide 3-kinases (PI3K) and the mammalian target of rapamycin (mTOR).
Kathrin Thedieck did her postdoctoral training with Michael N. Hall (Basel University, CH), with whom she discovered mTOR interactors that control cancer cell survival. These efforts laid the foundation for her work done at Freiburg University where she started her own lab in 2008, and extended her efforts to develop systems approaches to the PI3K/mTOR network.
In the frame of the e:Med projects GlioPATH (coordinator: Dr. C. Opitz, DKFZ, Heidelberg) and MAPTor-NET (coordinator Prof. Dr. Sers, Charite, Berlin), Thedieck and colleagues are further developing this work with emphasis on precision therapies for cancer and genetic diseases.

Wed Nov 22 — Modelling in Systems Medicine

03:45- 04:00 pm

Clonal evolution in adult glioblastoma
Verena Körber

Verena Körber studied Molecular Medicine and Systems Biology at the Universities of Ulm and Heidelberg. In her Master thesis she developed mathematical models to describe the T cell immune response to vaccinia virus. She received her Master's degree in 2015 and then started her PhD with Prof. Thomas Höfer at the German Cancer Research Center (DKFZ) in Heidelberg. Verena Körber's research interests lie in the processes that govern cancer initiation and progression. As part of the SYS-GLIO consortium, she studies genetic heterogeneity along with the underlying evolutionary dynamics in glioblastoma. She is also interested in the transcriptional networks governing tumor initiation from neural stem cells.

Wed Nov 22 — General Data Protection Regulation

04:30 - 05:00 pm

General Data Protection Regulation (GDPR) and its consequences for research
Boris Reibach

- Fully Qualified Lawyer studies in Augsburg
- Master of Laws degree in Information Technology Law from Oldenburg University
- Previously consultant at several community law centers in Germany and New Zealand
- Since 2011 Attorney at Law specialising in data protection law and External Data Protection Officer for numerous companies in various industry sectors at Scheja & Partner Attorneys at Law, Bonn, Germany
- Since 2014 Research Assistant at Oldenburg University, specialising in data protection and IT law
- Regular speaker at national and international data protection conferences
- Certified Data Protection Officer

Thu Nov 23 — Systems Medicine Impulse Talks

09:00 - 09:30 am

Closing the translational gap – integrating of high-throughput data for personalized cancer treatments into clinical processes

Oliver Kohlbacher

Research in the group of Oliver Kohlbacher (Chair for Applied Bioinformatics) focuses on method development for the analysis of high-throughput data, immunoinformatics, and structural bioinformatics. A particular focus is on the analysis of mass spectrometric data (proteomics, metaproteomics, metabolomics), for which is group has been developing open-source software (OpenMS) for a long time. Integrating these approaches, automating analyses and bringing the resulting workflows to the clinical application has been another focus of recent years. Oliver Kohlbacher is also the director of the Quantitative Biology Center (QBiC) and a fellow of the Max Planck Institute for Developmental Biology in Tübingen.

09:30 - 10:00 am

Progressive fibrosis as driving force behind liver cirrhosis, liver failure and hepatocellular carcinoma

Peter Jansen

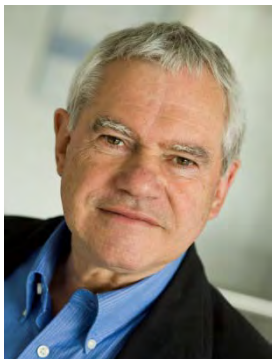
Peter Jansen is currently the program director of LiSyM, the Liver Systems Medicine research network in Germany. Peter Jansen is honorary professor at MaCSBio, the Maastricht Center for Systems Biology and he is emeritus professor of hepatology at the Universities of Amsterdam and Groningen.

He studied Medicine at the University of Nijmegen and received his PhD at the Institute of Pharmacology with work on drug metabolism in 1975. For part of his scientific training he went to the Albert Einstein College of Medicine in New York (1973-76). In 1986 he became associate professor at the AMC in Amsterdam and in 1993 he was appointed professor of hepatology and head of the department of Gastroenterology and Hepatology in the University Medical Center in Groningen, the main liver transplantation center in the Netherlands. In 2003 he returned to Amsterdam as head of the liver unit. Peter's research is devoted to trans-membrane ABC transport proteins, interaction between liver and intestine, FGF19-signalling, nuclear hormone receptors and the role of bile salts in cholestatic and metabolic liver disease.

Thu Nov 23 — Systems Medicine Approaches in Clinics

10:00 - 10:30 am

The German Network for Bioinformatics Infrastructure de.NBI Helps to Handle Big Data in Life Sciences
Alfred Pühler



A. Pühler studied Physics at the Friedrich-Alexander University Erlangen Nürnberg, got his Ph.D. degree in Microbiology in 1971 and habilitated in 1976. From 1980 until 2008, he was head of the Chair of Genetics at Bielefeld University. He is now running a Senior Research Group at the Center for Biotechnology at Bielefeld University. His research interests are focused on genome research of industrially relevant microorganisms and cell cultures. From 1999 to 2005, A. Pühler was member of the Science Council installed by the Federal President of Germany. He is member of three Academies, the North Rhine-Westphalian Academy of Sciences, the German Academy of Sciences Leopoldina and the National Academy of Science and Engineering (acatech). From March 2015 on, he coordinates the Germany network for Bioinformatics Infrastructure (de.NBI) funded by the BMBF. Since August 2016, he is appointed as Head of Node of ELIXIR Germany, the German node of the European Life-Science Infrastructure for biological Information.

Tue Nov 23 — Systems Medicine Approaches in Clinics

11:00 - 11:30 am

Keynote: Translational approaches for progressive diseases
Erwin Böttinger

Professor Dr. Erwin Böttinger is Professor and Chair of Digital Health and Personalized Medicine at the joint Digital Engineering Faculty of the Hasso Plattner Institute (HPI) gGmbH and the University of Potsdam. He is the founding director of the HPI Digital Health Center. From November 2015 to July 2017 Prof. Böttinger was Chairman of the Board of the Berliner Instituts für Gesundheitsforschung/Berlin Institute of Health (BIH). Prof. Böttinger is considered an international expert in personalized medicine and digital health, in particular from his services as founding director of the Charles Bronfman Institute for Personalized Medicine at the Icahn School of Medicine at Mount Sinai in New York, USA, from 2005 to 2015.

11:30 - 11:45 am

Updates on the ENIGMA-Epigenetics Working Group
Sylvane Desrivières

Sylvane Desrivières is Reader in Genetics at the Institute of Psychiatry, Psychology & Neuroscience at King's College London. Having earned her MSc and PhD in Molecular Biology from the University of Paris VII, she worked in outstanding institutions in Switzerland and Germany, studying how gene activity controls biological systems of increasing complexity, from individual cells and organs to the human brain. When in 2006, advances in magnetic resonance imaging (MRI) were such that measuring changes of the brain in vivo had become a reality, she took this exceptional opportunity to move her career forward, in a world leading university.
Leading Genetics Working Groups in several large international consortia, she since applies her skills to discover the genetic roots of neurophychological traits that may be disrupted in individuals suffering from mental illness, including addictions. This resulted in a remarkable portfolio of discoveries, with >65 publications in the past 10 years.

11:45 - 12:00 pm

Anti-TNFα restores disrupted metabolic interaction of the intestinal microbiome in IBD
Ateequr Rehman

Ateequr Rehman is working as a senior research scientist at the Institute of Clinical molecular biology, Christian Albrechts University Kiel, Germany. Combining the background of a classical microbiologist with state of the art next generation sequencing approaches, Dr. Rehman's research focuses on the role of gut microbial communities in the pathogenesis of complex intestinal diseases, especially in inflammatory bowel disease. His projects mainly apply high throughput sequencing approaches to investigate phylogenetic and functional interplay of intestinal microbiota in the context of disease, genotype and environmental perturbations, aiming to identify microbial communities influencing host health and disease status. As part of that, he majorly contributed to the understanding of risk gene associated microbiota in inflammation. Dr Rehman has co-authored 35 publications in peer reviewed journals, including the journals of high repute such as Nature, PNAS, Gastroenterology, Journal of Clinical Investigation and Gut.

12:00 - 12:15 pm

Multi-omics based strategy to predict graft function and personalize immunosuppressive therapy in kidney transplantation
Nina Babel

Professor Nina Babel is head of the Center for Translational Medicine at the Marien Hospital Herne, Ruhr-University Bochum and Principal Investigator at Berlin-Brandenburg Center for Regenerative Therapies, Charité-Universitätsmedizin Berlin. She studied Human Medicine at the Humboldt-University in Berlin, where she received her diploma in 1995.
She spent her Residence of Internal Medicine at Department of Nephrology and Internal Intensive Care at Charité, specialized in Transplant Medicine and worked as deputy head of Kidney Transplant Outpatient Clinic of Charité, Campus Virchow until 2015. She was recipient of the Rahel Hirsch Habilitation Fellowship and of a Fellowship at the Department Experimental Hematology at Taussig Cancer Center, Cleveland Clinic Foundation, Cleveland, USA, and habilitated in 2008 at Charité-Universitätsmedizin in Berlin.
Her prizes and honors include the Young investigator award of American Transplant Physicians, the Young investigator award of International Transplant Society, the Young Investigator Award of European Renal Association, the New key opinion leader of International Transplant Society, TTS, and the Award of European Renal Association.

02:15- 02:45 pm

Keynote: Pharmacogenomics: from translational research to next generation benefit-risk evaluation
Julia Stingl

Julia C Stingl (formerly Kirchheiner) M.D. is professor of translational pharmacology at the University Bonn Medical Faculty and head of the research division of the Federal Institute of Drugs and Medical Devices. Since 2014 she is Vice President of the institute.
Her research focuses on individualized drug treatment optimized by pharmacogenetics. She developed dose adjustments based on differences in drug clearances caused by pharmacogenetic polymorphisms promoting the way of pharmacogenetics from bench to bedside. She explored genetic influences on drug response and worked on characterization of the physiological role of genetic polymorphisms. She integrated new pharmacogenetic methods such as brain imaging techniques for visualization of pharmacogenetics modulation of individual drug effects. She has more than 190 peer-reviewed scientific publications, has been cited more than 6200 times with an average citation of 25 per article and an H-index of 43 (ISI web of science, August 2017).

02:45 - 03:00 pm

Integrating multi-omics and multi-modality medical imaging to assess hepatocellular carcinoma patient outcome under Sorafenib treatment: A progress report of the Multiscale HCC project
Mathew Divine

Born in California and raised in Texas, I completed my Bachelor's Degree in Physics and Mathematics at Midwestern State University in Texas before coming to Germany in 2007, where I earned a Master's in Biomedical Engineering at the RWTH in Aachen in 2010.
I completed my doctorate at the Werner Siemens Imaging Center in Tübingen in 2016, where I was involved in the entire preclinical molecular imaging pipeline from the conception of experiments to the implementation and analyses of the multi-dimensional biomedical imaging data. This work resulted in a novel model of tumor growth in a preclinical cancer model as well as semi- and un-supervised models of tissue heterogeneity in tumors.
I am currently a Post-Doc at the Applied Bioinformatics Group in Tübingen. My duties as part of the MultiscaleHCC project include collecting and analyzing heterogeneous data sets resulting from biomedical imaging and multi-omics measurements on patients with unresectable hepatocellular carcinoma. I am currently working on a predictive model for patient therapy stratification.

03:00 - 03:15 pm

"Systems hematology" – Opportunities, benefits, and limitations
Ingo Roeder

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Prof. Ingo Roeder studied mathematics at the TU Dresden (diploma in 1994) and got his PhD (2003) in theoretical biology at the University Leipzig. From 2003 till 2010 he was head of an independent research group on "Dynamical modelling of stem cell organization" at the Faculty of Medicine, University Leipzig. Since 2010, he is director of the Institute for Medical Informatics and Biometry, which is part of the Carl Gustav Carus Faculty of Medicine at the Technische Universität Dresden and he holds the chair for Medical Statistics and Biometry. In 2015 Prof. Roeder became scientific head of the Data and Trial Management Unit (DTMU) at the National Centre for Tumor Diseases (NCT) at the partner site Dresden. Furthermore, he is leader of the working group Computational Stem Cell Biology within the German Stem Cell Network (GSCN) and project committee member of the e:Med Systems Medicine initiative of the Federal Ministry of Education and Research.

Thu Nov 23 — Systems Medicine Approaches in Clinics

03:15 - 03:30 pm

How to report somatic variants in molecular tumor boards
Tim Beißbarth

Tim Beißbarth is leading the Statistical Bioinformatics group at the Department of Medical Statistics of the University Medical Center Göttingen. Tim Beißbarth studied biology and computer science in Cologne, did his PhD in the Theoretical Bioinformatics group at the German Cancer Research Center in 2001 and worked in Berlin, Melbourne (Autralia) and Heidelberg before becoming an associate professor in Göttingen in 2008. The focus of his group is the development of methods and tools to analyse and integrate biomedical data, such as next-generation sequencing and proteomics data, and to apply these in inderdisciplinary collaboration projects. The group is taking part in several e:Med funded consortia, namely MMML-Demonstrators, HER2Low, the ELSA consortium Genoperspektiv and the i:DSem consortium MyPathSem. Also, the junior research group of Frank Kramer established through the e:Med MultiPath project originates from the statistical bioinformatics group.

Thu Nov 23 — Closing Remarks

03:30 - 03:45 pm

Karsten Rippe, Speaker e:Med Project Comittee

Professsor Dr. Karsten Rippe is spokesperson of the e:Med project committee and since April 2007 group leader of the Research Group Genome Organization & Function at the German Cancer Research Center (DKFZ) and the BioQuant in Heidelberg. He is head of the e:Med consortium for systems medicine CancerTelSys, identifying cancer telomere maintenance networks for diagnosis, prognosis, patient stratification and therapy response prediction.

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Oral Presentations

Satellite Symposium
on Technological Innovations

Unraveling the tumor microenvironment architecture by multispectral imaging

Presenting Author: Angela Vasaturo

Integrative Cancer Immunology, Cordeliers Research Center Paris, France

Sponsored by Perkin Elmer

The natural history of cancer involves interactions between the tumor and the immune defense mechanism of the host. The crucial role of the patient's own immune system on clinical outcome is demonstrated by the immunological characterization of the tumor microenvironment. The analysis of type, location and density of tumor infiltrating immune cell components has identified immune cell types that can be either beneficial or harmful to patients showing also that immune cells can infiltrate the core (center) of the tumor and/or remain located in peritumoral areas and that lymphocytic infiltration of tumor or peritumoral tissue can be a favorable prognostic factor in a range of tumor types. In order to better understand the tumor microenvironment and its architecture, recent advances in the field of tissue imaging resulted in the development of multispectral imaging and analysis of up to six immunofluorescence markers within intact tissue sections. This novel technique combines imaging with spectroscopy allowing quantitative assessment of cellular phenotype and activity in a way similar to flow cytometry, while simultaneously providing tissue context and information about cell-to-cell usually difficult or impossible to obtain by other methods. We developed different 7-plex immunofluorescence multispectral panels and applied this novel technology to multiple tumor types in order to identify and quantify the densities of different immune cell subtypes. Furthermore, we have developed an analytical pipeline for first- and second-order spatial analysis of multispectral imaging data, which enables a high-definition characterization of the tumor microenvironment architecture including the spatial distribution of the different immune cell subtypes.

Follow response to treatment by single-cell sequencing

Presenting Author: Philipp Mallm

DKFZ Heidelberg

Sponsored by 10x Genomics

Cancer can arise in almost any tissue in the human body. Single-cell analysis in cancer may yield insights into the functioning and development of human cells and tissues both in health and diseased conditions. Furthermore, distinct subpopulations may respond differently to treatment and external stimuli, which cannot be detected in bulk sequencing approaches.

During my talk I will present data generated with the 10X Genomics Chromium platform to dissect tumor subpopulations, response to therapeutic intervention and aging processes. 10X Genomics uses the Drop-seq method by encapsulation single cells in oil droplets and capturing RNA molecules on beads with subsequent cDNA synthesis. Workflows from sample to data analysis will be discussed.

With this technique we were for instance able to detect certain gene signatures that may predict the responsiveness to treatment in Multiple Myeloma patients.

Unravelling cellular heterogeneity - A single cell biology approach

Presenting Author: Andreas Schlitzer

University of Bonn

The advent of single cell technologies, such as single cell mRNA sequencing, single cell ATAC sequencing, high dimensional flow cytometry and mass cytometry has allowed to study the organization of the immune system with unprecedented resolution. Myeloid cells are amongst the most heterogeneous cellular entities of the immune system and the current technological advances allow a new, single cell resolution, understanding of these important cell types. The lab, in cooperation with the Platform for Single Cell Transcriptomics and Epigenomics of the German Centre for Neurodegenerative Disease and the University of Bonn (PRECISE), employs a range of single cell biology approaches to understand the complexity of the myeloid cell system during health and disease. Here I will present an integrated single cell biology approach to better understand the development, heterogeneity and functional polarization of human and mouse monocytes, which allows a better, more tailored, clinical use of this important cell type.

High resolution single cell analysis in complex adult tissues

Presenting Author: Stefan Günther
Sponsored by WaferGen

Günther S., Yekelchyk M., Salwig I., Preussner J. and Braun T

Max-Planck-Institute for Heart- and Lung Research, Bad Nauheim
ECCPS Bioinformatics and deep sequencing platform
AG Braun

Molecular analysis of complex tissues in adult model organisms is a common tool for deciphering processes and networks during development, aging and disease. The majority of such “omic” analyses were done using whole tissue/organs or in macro or micro dissected anatomical regions. However, the complexity and cellular composition of such samples prevent high-resolution analysis. Identification of small subpopulations or specific changes within small cell populations are usually not detected due to massive overrepresentation of signals/data points from bulk cells. To overcome these problems and to gain insights into subpopulation of cells many attempts are being made to switch from bulk analyses to identification of molecular changes in single cells. This approach allows a very high-resolution analysis, but is associated with numerous other problems that have to be resolved to achieve meaningful insights. Our main focus is on the transcriptomics of individual cells and subpopulations. Many techniques and tools were developed during last years to obtain transcriptomics data from hundreds or thousands of cells from different model organisms, organs and tissues. Nonetheless, many experiments require special tissue-dependent conditions limiting the use of standard methods. Here, we show data from 2 projects, which faces special challenges regarding cell size and number of cellular subpopulations within individual samples. In collaboration with Wafergen/Takara Bio we demonstrate that the ICELL8™ Single-Cell System can be used to obtain high-resolution single cell data for particularly large cells or complex cell populations, which are difficult to analyze with other techniques. Our results provide new insights into the heterogeneity of cell populations and the transcriptional networks that regulate biological processes in the corresponding tissues.

Oral Presentations

Systems Medicine Visionary Talk

Visionary talk: Design principles of circuits for tissue homeostasis

Presenting Author: Uri Alon

Weizmann Institute, Israel

Tissues maintain a total tissue size that provides desired function, and also maintain the proportions between cells of different types . How this homeostasis of size and composition is maintained is a current research challenge. I will describe progress in understanding which circuits of cells, that communicate by secreted factors, can maintain robust homeostasis. Theory and experiment suggest that the number of possible circuits is small, providing hope that different tissues use similar principles (although with different cell types and molecules). I will also describe how such circuits can be robust to takeover by mutants that mis-read the signals, by means of biphasic responses in which the signal is toxic at both high and low levels (eg glucotoxicity, neuronal excitotoxicity). Just as systems biology identified the recurring circuits inside cells, such as coherent and incoherent feedforward loops, it is possible to foresee a field of tissue-level systems biology, that can provide a language to understand circuits of communicating cells for tissue function and homeostasis.

e:Med
SYSTEMS MEDICINE

Oral Presentations

Technologies in Systems Medicine

Keynote: LEAN analysis biological network hot spots in the age of Big Data

Presenting Author: Benno Schwikowski

Institut Pasteur, Paris

Molecular networks are emerging as useful scaffolds for statistical discoveries in genome-scale datasets, such as transcriptomic data. As new experimental technologies and resulting larger datasets proliferate, the opportunities for the computational discovery in these large datasets increase.

It is a lesser-known fact that, with the increase in data size, also the theoretical difficulty of the computational analysis problem may outpace any current advances in computational technology, rendering practical solutions of the problem infeasible, and enforcing us to rethink the biological patterns we search for.

In my talk, I will argue that the well-known problem of 'hot spot detection', i.e., the statistical detection of subnetworks with high aggregate biological signal has arrived at this point. I will show why this is not just a problem of any particular algorithm or method, but a fundamental problem with the underlying search pattern.

Following this insight, we developed Local Network Analysis (LEAN), based on a simplified search pattern. I will discuss the method and its validation, as well the application of the new search pattern to transcriptomic data in a mouse model of a human genetic disease, Cerebral Cavernous Malformations. LEAN analysis of this data led to an unexpected biological hypothesis, and an unexpected insight about the importance of an additional, originally unintended, but very useful, feature of LEAN that may add to its usefulness as a tool for biological discovery in the future.

Metabolomic Changes in Lymphoma in Response to Stromal Stimuli

MMML-Demonstrators

Presenting Author: Wolfram Gronwald

Paul Heinrich1, Maren Feist2, Xueni Sun1, Philipp Schwarzfischer1, Annkatrin Arlt2, Dieter Kube2, Peter J. Oefner1, Katja Dettmer1, Wolfram Gronwald1

1Institute of Functional Genomics University of Regensburg, 93053 Regensburg, Germany; 2Clinic of Haematology and Medical Oncology, University Medical Centre Göttingen, 37099 Göttingen, Germany

Lymphoma cells have an altered metabolism compared to normal B-cells, at least partly due to overexpression of the transcriptional amplifier c-Myc. In addition, we have observed that STAT3/NF-kB activity due to external stimuli such as IL10 and CpG might substitute aberrant c-Myc, suggesting that intracellular metabolism is decisively regulated by the lymphoma microenvironment. One of the key questions in this context is whether c-Myc and STAT3/NF-κB show the same effects on the metabolism of lymphoma cells. As glutamine is one of the key metabolites in this context, we have developed a set of stable isotope based metabolic flux experiments that allow us to follow its intracellular fate in detail. Specifically, based on uniformly 13C labeled glutamine we can monitor incorporation of its atoms in intermediates of the TCA as well as in amino acids. Employing 13C1 labeled glutamine, we could further show that glutamine also fuels reductive carboxylation under Mychigh conditions and in Myclow cells stimulated with IL10 and CpG. To follow the use of glutamine for nucleotide synthesis, experiments based on 15N labeled glutamine were developed. To correct in this context for the effects of naturally occurring stable isotopes, specifically in case of MS/MS experiments, a novel software tool was developed. To further elucidate the interplay between lympoma cells and their microenvironment we investigated how the secretome of tumor cells affects the metabolism of macrophages and vice versa. We could show that the secretomes of different tumor lines have distinct differential effects on monocyte derived macrophages. In summary, these findings may eventually lead to novel therapeutic options in the treatment of lymphoma.

Spatial organization of B cells and T cells predicts loss of renal transplant function

SYSIMIT

Presenting Author: Katharina Nekolla

Katharina Nekolla (1) Ralf Schönmeyer (1) Nadine Sarah Schaadt (2) Carolina Vanegas (1) Armin Meier (1) Arno Schäpe (1) Victor Matvienko (1) Nicolas Brieu (1) Wilfried Gwinner (3) Günter Schmidt (1) Friedrich Feuerhake (2)

(1) Definiens AG, Munich, Germany (2) Institut für Pathologie, Medizinische Hochschule Hannover, Germany (3) Klinik für Nieren- und Hochdruckerkrankungen, Medizinische Hochschule Hannover, Germany

Immuno-oncology has shown that the assessment of the spatial context of tumor-infiltrating immune cells (ICs) beyond cell density offers improved prognostic value. By applying Tissue Phenomics we investigated whether similarly the spatial distribution of ICs in relation to anatomical structures in renal transplant biopsies can be associated with loss of transplant function and thus can improve existing scores guiding clinical decisions. In a longitudinal study with 54 renal transplant patients, needle biopsies were obtained in a protocol biopsy program at multiple prescheduled time points. Sections were dual-stained for CD3 and CD20 and digital whole slide images (WSI) were acquired. CD3+ T cells and CD20+ B cells were detected using a weakly supervised machine learning method. A convolutional neural network (CNN; Caffe framework) was trained to automatically detect glomeruli, using annotations provided by pathologists as ground truth. Image-based features were defined to describe the spatial distribution of CD3+ and CD20+ cells near glomeruli (distance<300um). The features were used to train a decision tree (DC) classifier to predict the future status of the transplant function (glomerular filtration rate reduced (<60) or normal (>=60)) one to two years after the biopsy. The prediction accuracy of the CNN to detect glomeruli yielded an F1 score of 0.9. A 10-fold cross-validation of the DC classifier (depth=2) showed an average accuracy of 0.8 to predict the future transplant function. The classifier decisions are based on T cell clustering and average distances of T cells and B cells to the nearest glomerulus. We show that phenomic information such as spatial organization of IC populations can serve as an early predictor of future renal transplant function. The study suggests that existing prognostic factors may be complemented with tissue-based immune profiling to improve clinical decision making and therapy success in transplantation medicine as well as oncology.

Introducing the de.NBI Cloud – the novel compute and storage infrastructure for life sciences

de.NBI

Presenting Author: Chris Lawerenz

C. Lawerenz1, A. Goesmann2, B. Grüning3, J. Krüger4, A. Sczyrba5

1Theoretical Bioinformatics, German Cancer Research Center (DKFZ), Heidelberg
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In life sciences today, the handling, analysis and storage of enormous amounts of data pose a challenge to many researchers. For example, new sequencing and imaging technologies result in the generation of large scale genomic and image data, which require powerful compute infrastructure for subsequent analyses.

The de.NBI Cloud (www.denbi.de/cloud) provides appropriate IT infrastructure to perform analyses with such large datasets and ensures secure data access and storage. To a large extent, the de.NBI Cloud will close the gap of the missing computational resources for life science researchers in Germany.

The de.NBI Cloud is a fully academic cloud, free of charge for academic users. All resources (i.e. hardware and personnel, IT administration and operation, as well as deployment of operating systems, frameworks, and workflows) are provided by the five cloud centres at the universities of Bielefeld, Freiburg, Gießen, Heidelberg, and Tübingen.

Through a cloud federation concept, the de.NBI sites are integrated into a single cloud computing platform. The user will be guided to the anticipated service and the suitable cloud via the central de.NBI Cloud Portal. The whole system is accessible through single sign-on (SSO) and is based on the ELIXIR Authentication and Authorization Infrastructure (ELIXIR-AAI).

We will present the de.NBI Cloud on the e:Med meeting 2017: de.NBI Cloud experts will be available at the de.NBI information booth during the meeting. e:Med participants will be introduced on how to use the cloud during hands-on demos.

e:Med
SYSTEMS MEDICINE

Oral Presentations

Systems Medicine in European Context

SYSCID – A systems medicine approach to chronic inflammatory diseases

SysINFLAME

Presenting Author: Philip Rosenstiel

Institute of Clinical Molecular Biology (IKMB) and 1st Department of Internal Medicine, University Hospital Schleswig-Holstein (UKSH) Kiel and Christian-Albrechts-University Kiel

Chronic inflammatory diseases (CID) comprise a group of disorders of the immune system with a lifetime prevalence of over 10% in the EU and a continuously rising incidence in Western countries. Despite different clinical manifestations, CID show a vast overlap of genetic risk maps and environmental risk factors.
SYSCID is a H2020 funded large scale network concentrating on personalized medicine in CID. The talk will outline SYSCID´s major focus areas to identify a common set of mechanisms and blood-based biomarkers that contribute to the pathogenesis of three exemplary CIDs: inflammatory bowel disease, systemic lupus erythematodes and rheumatoid arthritis. Improved predictability will guide therapy decisions on an individual patient level enabling the choice of the right therapy at the right time. At the same time, SYSCID will investigate the development of new causative therapies by editing the epigenome and transcriptionally reprogram specific cell types. Unlike current therapeutic interventions which only alleviate the symptoms, SYSCID also aims to develop epigenetic reprogramming strategies, that may lead to new targeted and causal therapeutic principles. SYSCID has several strategic links to international consortia in genomic disease research. The talk will present strategies of SYSCID and discuss potential synergies with the national e:Med systems medicine program.

German imaging science in European context

Multiscale HCC

Presenting Author: Bernd Pichler

Werner Siemens Imaging Center, University Hospital Tübingen

Medical Informatics Initiative and Systems Medicine Initiative – An opportunity not to miss –

CAPSyS

Presenting Author: Markus Löffler

University of Leipzig

The Medical Informatics Initiative (MII) is a large scale and prolonged BMBF funding initiative to promote the digitalization in the health sector and enable novel ways of making medical record data accessible for research and to integrate novel types (eg genetic and image) data into patient care and clinical decision making. The initiative also promotes novel ways of data sharing and distributed computing as well as patient participation.

The MII starts in 2018 with 4 consortia creating alliances of university hospitals, academic institutions and partners form the IT-industry. I will report about the strategy of one of the consortia which I chair (SMITH) and about the overarching alliance with the other three. This initiative will open highly interesting perspectives to integrate systems medicine approaches, models, decision support systems and data analysis tools finally into the clinician desk top. I will illustrate how we like to include some of out e:Med projects into this translation process in SMITH.

It is my aim to make the systems medicine community aware of this emerging opportunity in Germany.

Oral Presentations

Systems Medicine of Diseases

Keynote: Frontostriatal mechanisms of anhedonia in novel neurophysiological subtypes of depression

Presenting Author: Conor Liston

Weill Cornell Medical College, NYC, USA

Biomarkers have transformed modern medicine but remain largely elusive in psychiatry, partly because there is a weak correspondence between diagnostic labels and their neurobiological substrates. Like other neuropsychiatric disorders, depression is not a unitary disease but rather a heterogeneous syndrome encompassing varied, co-occurring symptoms and diverging responses to treatment. Using functional magnetic resonance imaging (fMRI) in a large multisite sample (N=1,188), we showed that patients with depression can be subdivided into four neurophysiological subtypes defined by distinct patterns of dysfunctional connectivity in limbic and frontostriatal networks. Clustering patients on this basis enabled the development of biomarkers (statistical classifiers) for diagnosing depression subtypes with high (82-93%) sensitivity and specificity in multisite validation (N=711) and out-of-sample replication (N=477) datasets. These subtypes cannot be differentiated based solely on clinical features, but they are associated with differing clinical symptom profiles. They also predict differential improvements in anhedonia, anxiety, and other depressive symptoms in response to transcranial magnetic stimulation of the dorsomedial prefrontal cortex (N=154). To further understand the circuit mechanisms underlying one of these subtypes, we used optogenetic tools and two-photon calcium imaging to interrogate frontostriatal circuit function in a mouse model of chronic stress. Our results indicate that dysfunctional connectivity in frontostriatal circuits suppresses striatal responses to reward-related VTA signals, impairing the expression of reward-seeking behaviors. Together, these findings define novel subtypes of depression that transcend current diagnostic boundaries and may be useful for identifying individuals most likely to benefit from targeted neurostimulation therapies.

Metabolomics in Translational Medicine – A Link between Acylcarnitines and Atrial Fibrillation

symAtrial

Presenting Author: Julia Krause

Krause J.1,2, Löser A.2,3, Börnigen D.1,2, Matthias Heinig 4, Ines Assum 4, BiomarCaRE consortium 1, Schnabel R.1,2, Markus Scheinhardt 5, Blankenberg S.1,2, Eschenhagen T.2,3, Stenzig J.2,3, Zeller T.1,2

1 University Heart Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 2 DZHK (German Center for Cardiovascular Research), partner site Hamburg/Kiel/Lübeck, Hamburg, Germany; 3 Department of Experimental Pharmacology and Toxicology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, 4 Institute of Computational Biology, Deutsches Forschungszentrum für Gesundheit und Umwelt, Helmholtz Zentrum München, 85764 Neuherberg, Germany, 5 Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, Universitätsklinikum Schleswig-Holstein, Lübeck, Germany.

Objective: Atrial fibrillation (AF) is the most common arrhythmia and associated with an increased risk of stroke. The molecular mechanisms leading to AF still remain largely unknown. We aim to use metabolomics data to identify and analyze relations between metabolites and AF in a systems medicine approach.

Methods: Metabolomic profiles were generated in serum samples by mass spectrometry using the p180 kit in 632 incident AF cases and 9028 non-cases within the European BiomarCaRE project. Replication was performed in serum and tissue samples of 118 prevalent AF cases and controls from the Atrial Fibrillation Clinical Cohorts study (AF_CCS). The statistical analysis involved Cox proportional hazard models to assess the associations between metabolites and AF, adjusted for classical cardiovascular risk factors. Rat ventricular engineered heart tissue (EHT) were stimulated with different metabolite levels of the identified metabolite for two weeks and force, shortening, contraction and relaxation velocity were measured.

Results & Conclusion: We identified a mono-unsaturated long-chain acylcarnitine (AC) as a plasma metabolite significantly associated with a higher risk of AF. During treatment of ventricular rat EHTs with AC, we observed a significant dose- and time dependent effect resulting in an impaired contractility, arguing for a pro-arrhythmic effect of AC rather than an association only. To account for the differences between atrial and ventricular cardiomyocytes, we have established an atrial EHT model to consider AF. Furthermore, we generated transcriptome and proteome data from the tissue samples of the AF_CCS with the aim to identify potential pathways which explain the accumulation and role of the identified AC in AF.

Reconstruction of tumor evolution from massively parallel sequencing data

SMOOSE, MILES

Presenting Author: Nima Abedpour

Nima Abedpour (1), Carmen Herling (2), Julie George (1), Martin Peifer (1,2)

(1) Department of Translational Genomics, Center of Integrated Oncology Cologne–Bonn, Medical Faculty, University of Cologne, Cologne, Germany; (2) Department of Internal Medicine I, Center of Integrated Oncology Cologne-Bonn, University of Cologne, Cologne, Germany; (3) Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany

Understanding the principles underling cancer evolution is crucial for predicting cancer progression and therapeutic responses. The common belief is that cancer evolves by accumulation of somatic mutations under a complex process of diversification and selection. Rapid advances in high-throughput sequencing technologies led to the necessity of computational methods for reconstructing evolutionary processes from sequencing data. We developed computational techniques to infer the evolution of copy number changes and to reconstruct the phylogeny of subclonal populations from bulk tumor sequencing data. These developments were applied to whole-genome sequencing data of more than 100 small cell lung cancer samples (George et al., Nature 2015). Among the inferable copy number alterations, we found that copy neutral loss of heterogeneity evolves at two bursts of early and late stage in tumor evolution, while single copy number gains mostly appeared at a later stage in the evolution of the cancer cells. Restricting our analysis to the TP53 and RB1 locus provided us a model of the evolution of mutations affecting TP53 and RB1, which occur at a nearly universal rate in small cell lung cancer (George et al., Nature 2015). In addition, we analyzed whole-exome-sequencing data of 8 chronic lymphocytic leukemia patients that developed resistance upon BCL2-inhibition with the drug venetoclax. We identified recurrent mutations in BTG1 (2 patients) and homozygous deletions affecting CDKN2A/B (3 patients) that developed during treatment, as well as a mutation in BRAF and a high-level focal amplification of CD274 (PD-L1). By reconstructing the phylogenetic trees of clonal evolution for each patient, we obtained insights into the diverse evolutionary dynamics leading to venetoclax resistance.

Transcriptomic landscape of Pancreatic Cancer and normal Epithelial and Stromal cells directly isolated from human samples reveals common and cell-type specific deregulated nodes

PANC-STRAT

Presenting Author: Elisa Espinet

Elisa Espinet1,2, Zuguang Gu3,7, Charles D. Imbusch4, Vanessa Vogel1, Corinna Klein1, Jing Yang3, Octavio Espinosa3, Nathalia A. Giese5, Oliver Strobel5, Thilo Hackert5, Alexander Muckenhuber6, Matthias Schlesner3, Benedikt Brors4, Marcus Büchler5, Roland Eils3,7,8, Wilko Weichert6, Martin R. Sprick1,2 and Andreas Trumpp1,2

1 HI-STEM - Heidelberg Institute for Stem Cell Technology and Experimental Medicine gGmbH, Heidelberg, Germany 2 Division of Stem Cells and Cancer, DKFZ, Heidelberg, Germany 3 Division of Theoretical Bioinformatics, DKFZ, Heidelberg, Germany 4 Division of Applied Bioinformatics, DKFZ, Heidelberg, Germany 5 Department of General and Visceral Surgery, University Hospital Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany 6 Institute of Pathology, University Hospital Heidelberg 7 Heidelberg Center for Personalized Oncology (DKFZ-HIPO), Heidelberg 8 Department of Bioinformatics and Functional Genomics, Institute for Pharmacy and Molecular Biotechnology (IPMB) and BioQuant, Heidelberg University

Despite promising results using in vitro systems or genetically engineered mouse models new drug candidates have disappointingly failed to treat Pancreatic Ductal Adenocarcinoma (PDAC) patients in clinical trials. This shows that current models used at the bench might not fully recapitulate the human scenario and highlights the urgent need for a better understanding of the complex signalling taking place in human tumors. Expression analysis of human bulk tumor samples leads, however, to difficult and sometimes misleading results due to extensive presence of stromal cells (desmoplastic reaction). The detailed analysis of the epithelial-stromal interactions occurring in primary samples seems critical for better understanding PDAC complexity and to help therapy development. We have generated high quality RNA-Seq data from the major different cell populations present in PDAC tumors (i.e. Epithelial, Immune, Stromal and Endothelial cells) by FACS sorting fresh primary patient tumors. Using these data we have revised the contribution of different cell types to known pathways involved in PDAC. Additionally, using network analyses we have identified novel interactions taking place between different cell types. Last, we have generated RNA-Seq data from the corresponding cell-types in normal pancreas. This has allowed us to investigate the genes and pathways deregulated during PDAC tumorigenesis at cell-type level. To our knowledge this is the first study that approaches the study of PDAC tumor-stromal interactions using purely primary human material at such deep level of information as the one provided by RNA-Seq methodology. Understanding which cellular compartment is involved in which signalling process is of high relevance both to better understand PDAC tumorigenesis and provides critical information to develop more efficacious therapy concepts.

Multi-omics analysis methods for the genetic diagnosis of rare diseases

mitOmics

Presenting Author: Vicente Yépez

Vicente Yépez (1), Laura Kremer (2), Daniel Bader (1), Christian Mertes (1), Tobias Haack (3), Holger Prokisch (2), Julien Gagneur (1)

(1) Technical University of Munich, (2) Helmholtz Zentrum Munich, (3) University of Tübingen

Across a variety of Mendelian disorders, ~50–75% of patients do not receive a genetic diagnosis by exome sequencing indicating disease-causing variants in non-coding regions. Although genome sequencing in principle reveals all genetic variants, their sizeable number and poorer annotation make prioritization challenging. Here, we investigated the integration of exome and genome sequencing, together with RNA sequencing and quantitative proteomics to improve the diagnostic rate of mitochondriopathy patients. Our approach allowed to molecularly diagnose more than 10% of unsolved patients and identify candidate genes for the remainder. Quantitative proteomics was helpful to identify destabilized protein complexes and to confirm the functional impact of aberrant RNA expression. We observe that private exons often arise from cryptic splice sites providing an important clue for variant prioritization. One such event is found in the complex I assembly factor TIMMDC1 establishing a novel disease-associated gene. In conclusion, our study expands the diagnostic tools for detecting non-exonic variants and provides examples of intronic loss-of-function variants with pathological relevance.

e:Med
SYSTEMS MEDICINE

Oral Presentations

Modelling in Systems Medicine

Keynote: From Ideas to Medicine – with Modelling and Simulation

Presenting Author: Antje Walz

Translational Modelling & Simulation, Pharma Research and Early Development,
Roche Innovation Center Basel, Switzerland.

Modelling and Simulation (M&S) has become an integral part of the drug discovery and development process. Two case examples are presented illustrating how M&S approaches are recognized to enable a continuous learning process across the value chain, to support decision making and to increase the success rate of drug approvals.

First-in-Human (FIH) studies with anticancer drugs differ from other Phase I studies in that they are mainly evaluated in patients whose disease condition is progressive and fatal. The Food and Drug Administration (FDA) guideline for anticancer pharmaceuticals defines “the goal of selection a starting dose is to identify a dose that is expected to have pharmacological effects and is reasonably safe”. The first study case illustrates how mechanistic M&S approaches provide insights into the mode of action and how these approaches can be applied to guide biomarker selection and eventually optimal dose selection in early clinical trials.

Many anticancer drugs have a narrow therapeutic window. The second case study shows how translational M&S for both efficacy and safety can be applied to select the most favorable dosing regimen in humans. A translational model was developed to predict drug-induced thrombocytopenia. Simulations were conducted to explore the impact of different dosing regimens on the anticipated therapeutic window in cancer patients. With this approach, an optimal dosing regimen was selected with improved tolerability and a higher chance of success to reach efficacious exposure in cancer patients.

Predicting sensitivity of malignant melanoma to combination therapies by network modeling

Melanoma sensitivity

Presenting Author: Dagmar Kulms

Ines Müller1, Greta Del Mistro1, Christian Praetorius1, Friedegund Meier1, Philippe Lucarelli2, Thomas Sauter2, Martin Siegemund3, Roland Kontermann3, Markus Rehm3, Dagmar Kulms1

1Experimental Dermatology, Department of Dermatology, TU Dresden; Faculty of Science, 2Technology and Communication, University of Luxembourg; 3Institute of Cell Biology and Immunology, University of Stuttgart

Dysregulation of mitogen-activated RAS-RAF-MEK-ERK and PI3K-AKT-PTEN signalling pathways represent major inducers of melanoma development and progression, especially when constitutively activating point mutations of the proto-oncogenes BRAFV600 and NRAS are present. In response to conventional targeted mutBRAF (Dabrafenib) and MEK (Tremetinib) inhibitors, malignant melanoma still represent with high relapse rates coinciding with pronounced metastatic outgrowth. Also combination of BRAF and MEK inhibitors adds only marginal benefit for patients with advanced tumor stage. Aiming to (re-)sensitize melanoma cells to trageted drugs by addition of apoptosis-inducing molecules we have developed a hexameric TRAIL receptor agonist based on a TRAIL-Fc- fusion protein (Fc-sc-TRAIL, IZI1551), which shows significantly increased bioactivity compared to conventional trimeric scTRAIL. The melanoma selectivity as well as bioactivity could be even enhanced upon fusion of IZI1551 with a scFv against the melanoma-associated antigen CSPG4/MCSP or HER3. IZI1551 was shown to kill melanoma cells more potently than targeted BRAF and MEK inhibitors in 2d cell culture as well as in 3d melanoma spheroids. In order to investagte the impact of lethal and sublethal IZI1551 doses on long term melanoma cell survival and tumor relapse we took an iterative approach that combines experimental studies and systems based modelling. We identified the signalling network of melanoma cells to be prone to modifications of the activation status of survival proteins, including NFκB, IκBα, AKT, ERK, and JNK, resulting in newly acquired resistance and enhanced migration and invasion potential. The relevance of different these parameters/interactions in the signal transduction network of parental versus conditioned cells could be reflected by our newly developed Probabilistic Logic Network, which is able to describe the differences and to identify sensitive nodes as potential therapeutic targets.

A drug - cytokine interaction map for lympho-proliferative disorders

SYMPATHY

Presenting Author: Peter-Martin Bruch

Peter-Martin Bruch1,2, Junyan Lu3, Malgorzota Oles3, Sophie Rabe1-3, Marta Stolarczyk1,2, Wolfgang Huber3, Thorsten Zenz1,2, Sascha Dietrich1-3

[1] Department of Medicine V, University Hospital Heidelberg, Heidelberg, Germany, [2] Molecular Therapy in Hematology and Oncology, National Center for Tumor Diseases and German Cancer Research Centre, Heidelberg, Germany, [3] European Molecular Biology Laboratory (EMBL), Heidelberg, Germany

Mutational landscapes of tumors have been comprehensively mapped, but functional annotation and relation to tumor phenotypes remains largely lacking. To understand determinants of drug response, we measured ex-vivo sensitivity of 249 blood cancers to 63 drugs alongside genome, transcriptome and DNA methylome analysis. This data set revealed unexpected disease-specific sensitivities for each studied blood cancer entity (CLL, T-PLL, MCL, FL, AML). Within chronic lymphocytic leukemia (CLL) patient samples, response to 61% of drugs was associated with ≥ two mutations or copy number alterations. For instance, B-cell receptor (BCR) pathway activity was linked to trisomy 12, an important CLL driver. Drug responses partitioned phenotypic groups, for instance, 15% of CLL were driven by mTOR signaling non-BCR dependently. These subgroups were characterized by a distinctive mutation-, gene expression- and DNA methylation profile. Although very informative, this platform relies on a short-term culture model, which neglects signals provided by the microenvironment. Soluble factors (e.g. cytokines, chemokines) specifically modify or circumvent pathway activities that are therapeutically targeted. Moreover, lymphoma and leukemia cells undergo spontaneous apoptosis in-vitro in absence of their microenvironment conditions. To systematically assess the effects of soluble factors of the lymph node or bone marrow niche on drug response, we culture malignant cells in 18 different cytokine versus 15 clinically relevant drug conditions across 200 patient samples. We show that multiple cytokines either support in-vitro survival, sensitize or confer resistance to drug treatment. For instance, we demonstrate that activation of Jak/STAT3/STAT6 signaling interferes with response to ibrutinib. In summary, our setup will allow us to uncover microenvironment dependent pathway activities, which support survival or interfere with drug response in the genetic context of each individual patient.

Computational modelling of amino acid signaling to kinase networks

MAPTor-NET, GlioPATH

Presenting Author: Kathrin Thedieck

Daryl P. Shanley (1,2), Sascha Schäuble (3), Christiane A. Opitz (4,5), Christine Sers (6,7), and Kathrin Thedieck (8,9)

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Amino acids are not only building blocks for proteins, but also signaling molecules with key roles in cancer biology. The serine threonine kinase mammalian target of rapamycin (mTOR) is recognized as a key mediator of amino acid signals. We recently combined a computational-experimental approach with text mining-enhanced quantitative proteomics to identify further amino acid responsive kinases that act independently of mTOR. AMP-activated protein kinase (AMPK) emerged as being acutely activated by amino acids, and sustains autophagy under amino acid sufficiency. This may be required to maintain protein homoeostasis and deliver metabolite intermediates for cell cellular growth. In the frame of the GlioPATH and MAPTor-NET consortia we now unravel specific roles of distinct amino acids, and their interplay with mTOR and its ancillary signaling networks in driving cancer phenotypes and modulating drug responses.

Clonal evolution in adult glioblastoma

SYS-GLIO

Presenting Author: Verena Körber

Verena Körber1, Bernhard Radlwimmer2, Pankaj Barah3, Jing Yang3, Matthias Schlesner3, Katrin Lamszus4, Guido Reifenberger5, Michael Weller6, Peter Lichter2, Thomas Höfer1

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Glioblastomas are highly diffuse brain tumors with very poor prognosis. After surgical resection and/or cytotoxic therapy the tumor typically recurs within months. Here we analyzed 30 pairs of matched primary and relapse tumors with respect to the subclonal distributions of mutations (SNVs and CNVs) to inform target therapy approaches. Applying an inference algorithm to the sequencing read count distributions at mutated loci, we found that glioblastomas typically consist of at least two to three genetically distinct subpopulations. Our data further indicate that relapse tumors do not linearly evolve from subclones identified in the primary sample, but from common ancestor populations which are typically not recovered in the primary sample. Among the early, putatively tumor initiating events, we found few point mutations in classical oncogenes, but frequent copy number aberrations on chromosomes 7, 9 and 10. Fitting a dynamical model of tumor evolution to these data indicated that these early events primarily increase the cellular turnover rate, rather than driving tumor growth. Thus, the early phase of glioblastoma development is characterized by the accumulation of mutations and subclonal diversification, which only later result in accelerated tumor growth driven by several subclones. Our findings suggest that several aggressively growing subpopulations must be targeted to efficiently treat glioblastoma.

Oral Presentations

Datenschutzgrundverordnung

Der neue EU-Datenschutz: Folgen für die Forschung

Presenting Author: Boris Reibach

University of Oldenburg

Die Datenschutzanforderungen werden sich EU-weit zum 25.5.2018 ändern. Die neuen Vorgaben der Datenschutzgrundverordnung (DSGVO) sowie des reformierten Bundesdatenschutzgesetzes (BDSG) enthalten nicht nur allgemeine Regelungen zum Datenschutz, sondern auch spezifische Vorgaben für medizinische Datenverarbeitungen und die Forschung. Ihre Umsetzung muss zum Stichtag 25.5.2018 vollzogen sein. Um die Teilnehmer mit den Änderungen vertraut zu machen, werden die neuen Vorgaben für Praktiker der medizinischen Forschung anschaulich vorgestellt und ihre Auswirkungen auf die tägliche Arbeit erörtert. Während bei der DSGVO die EU-weit einheitlichen Standards angesprochen werden, wird auch auf die im BDSG enthaltenen Ausnahmen und Abweichungen eingegangen. Der Schwerpunkt liegt in der Sensibilisierung der Teilnehmer für die anstehenden Änderungen. Darüber hinaus sollen die Teilnehmer Hinweise erhalten, wie in der Praxis mit den komplexen und gleichzeitig oft auch abstrakt formulierten Anforderungen konkret umgegangen werden kann. Des Weiteren werden die rechtskonforme Einholung von Einwilligungen, der deutlich vergrößerte Katalog an Transparenz- und Auskunftspflichten sowie die erweiterten Haftungs- und Bußgeldrisiken thematisiert. Anschließend können im Rahmen einer Abschlussdiskussion Fragen und Fälle aus dem Publikum behandelt und erste Hilfestellungen gegeben werden.

Oral Presentations

Systems Medicine Impulse Talks

Closing the translational gap – integrating of high-throughput data for personalized cancer treatments into clinical processes

iD:Sem

Presenting Author: Oliver Kohlbacher

Center for Bioinformatics, University of Tübingen and Max Planck Institute for Developmental Biology, Tübingen, Germany

While the analysis of high-throughput data (genomics, transcriptomics, proteomics, etc.) has by now become routine in biomedical research, the integration into routine healthcare is progressing at a slower pace. We will discuss some of the issues when translating research ideas into clinical practice. In two showcases centered around personalized cancer treatment we will then discuss how IT systems can enable the implementation of personalized treatments. The first showcase is the implementation of personalized cancer vaccination, where multi-omics data needs to be integrated to enable a patient-specific design of an optimal vaccine. The second project is the development of interactive molecular tumor board solutions (funded within the iD:Sem initiative of BMBF) that will hopefully enable more interactive and efficient discussions of personalized cancer treatment options in general.

Progressive fibrosis as driving force behind liver cirrhosis, liver failure and hepatocellular carcinoma

Cirrhosis is as 'a wound that does not heal', except ...

LiSyM

Presenting Author: Peter LM Jansen

Professor of hepatology, University of Amsterdam
Program director LiSyM

Despite its unique capacity for regeneration and renewal, liver cirrhosis invariably develops when the causative toxic agent cannot be adequately removed or suppressed. Chronic exposure to steatosis, hepatitis B and C virus, alcohol and cholestasis eventually lead to cirrhosis, liver failure and hepatocellular carcinoma. In many of these diseases the lead-time from disease detection to liver transplantation or death is about 15-20 years. During these years relentless fibrosis indicates slow but steady disease progression. Non-invasive tests and techniques are available to follow fibrosis and disease progression.

Upon successful removal of the causative agent, the disease is halted and regeneration may lead to restoration of liver function. This phenomenon is well known in patients with alcoholic cirrhosis listed for organ transplantation. To become a candidate for transplantation patients have to stop using alcohol. This often leads to considerable recovery of liver function. Proof for liver regeneration, even at advanced disease stages, has also been shown in patients with sustained viral response after antiviral therapy.

For viral liver disease and alcoholic cirrhosis treatment rests on removal or suppression of the causative agent or condition. For non-alcoholic steatohepatitis (NASH) the situation is more complex. In NASH the offending toxic 'agent' is not known: steatosis and inflammation, the presence of lipotoxic fat species, or deranged metabolism with insulin resistance as underlying cause, may all play a role in cause and progression. Thus far there are no drugs to effectively suppress or remove the toxic 'agent' in NASH, if such 'agent' indeed exists. Effective drugs could be a game changer in this disease.

Since NASH is highly prevalent, a thorough understanding of the underlying causes and mechanisms is needed to find curative drugs. In the LiSyM research network we follow a systems medicine-based multidisciplinary approach to understand cause and mechanisms of NASH. NASH is studied in four multidisciplinary and geographically dispersed study groups: Pillar I 'early disease'; Pillar II 'cirrhosis, regeneration and hepatocellular carcinoma'; Pillar III 'acute-on-chronic liver disease'; Pillar IV biomarkers and special techniques to study disease progression.

LiSyM-supported research has provided clear examples of the power of computational modelling as an effective approach to advance our understanding of a complex disease.

The German Network for Bioinformatics Infrastructure de.NBI Helps to Handle Big Data in Life Sciences

de.NBI

Presenting Author: Alfred Pühler

de.NBI coordinator, CeBiTec, Bielefeld University, Germany

The 'German Network for Bioinformatics Infrastructure' (de.NBI) has been initiated by the Federal Ministry of Education and Research (BMBF) to meet the bioinformatic challenges in modern life sciences due to the rapid progress in analytical areas such as sequencing, 'omics' and imaging technologies. These technologies generate huge amounts of data, and thus require the access to well-maintained databases, bioinformatics tools, workflows and computing capacities. The mission of de.NBI is (i) to provide high-quality bioinformatics services to users in basic and applied life sciences research from academia, industry and biomedicine; (ii) to offer bioinformatics training to users in Germany and Europe through a wide range of workshops and courses; and (iii) to foster the cooperation of the German bioinformatics community with international network structures.

The 'German Network for Bioinformatics Infrastructure', consists of eight Service Centers located at German universities and research institutions. A coordinator and an administration office at Bielefeld University are responsible for the organization of the network. The broad spectrum of bioinformatics services ranges from the analysis of human, microbial and plant data to software libraries, data management provision and cloud computing. The de.NBI network organizes a large amount of training courses. In the current year, already 56 training courses with more than 1300 participants were arranged. Last year, Germany was integrated into the European Life-Science Infrastructure for biological Information ELIXIR, and the de.NBI network was asked to act as the national node. A further step forward was the establishment of a de.NBI cloud which is located at the universities in Bielefeld, Freiburg, Gießen, Heidelberg and Tübingen. Altogether, during the first 2 ½ years of its existence the de.NBI network developed to an important infrastructure which is well suited to solve the Big Data problem in Life Sciences. More information on the de.NBI network can be obtained from its web page www.denbi.de.

e:Med
SYSTEMS MEDICINE

Oral Presentations

Systems Medicine Approaches in Clinics

Keynote: Translational approaches for progressive diseases

Presenting Author: Erwin Böttinger

Hasso-Plattner-Institute, University of Potsdam

Updates on the ENIGMA-Epigenetics Working Group

SysMedAlcoholism

Presenting Author: Sylvane Desrivières

Sylvane Desrivières1, Tianye Jia1, Barbara Ruggeri1, Yun Liu2, Daniil Sarkisyan3, Ann-Christine Syvänen4, Tomas Axelsson4, Georgy Bakalkin3, Gunter Schumann1, the IMAGEN Consortium, Paul M. Thompson5 and the ENIGMA Epigenetics Working Group.

1Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom 2Department of Biochemistry and Molecular Biology, Fudan University, China 3Department of Pharmaceutical Biosciences, University of Uppsala, Sweden 4SNP&SEQ Technology Platform, Biomedical Centre, BMC, Uppsala, Sweden 5Imaging Genetics Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Epigenetic modifications like DNA methylation (DNAm) are major aetiological factors in neuropsychiatric disorders, including alcohol use disorders, that may be useful biomarker for these diseases even when measured in peripheral blood. So far, associations between blood DNAm levels, disease-related brain phenotypes, and adverse health outcomes were assessed in a few, small samples. We have created the ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) Epigenetics Working Group to make large-scale imaging epigenetic studies possible. We present here the first epigenome-wide association analyses of blood DNAm with volumes of the hippocampus, thalamus and nucleus accumbens. Associations of blood DNAm with structural T1-weighted brain magnetic resonance imaging scans from 3,337 individuals were analysed with harmonized protocols at 11 sites around the world and summary statistics meta-analysed. We identified 2 differentially methylated positions (DMPs) associating with volume of the hippocampus at experiment-wide false discovery rate < 0.05. Further analyses focusing on differentially methylated regions (DMRs) formed by clusters of neighboring CpG sites identified additional loci consistently associating with the volumes of the thalamus, hippocampus or nucleus accumbens in individual cohorts. Enrichment analyses of DMPs associated with hippocampal volumes revealed an overrepresentation of developmental genes associated high-CpG-density promoters bearing the repressive H3K27 histone tri-methylation mark in brain. Investigating of functional consequences of top DMPs and DMRs in individual cohorts revealed correlations between DNA methylation, expression of nearby genes, brain volume and cognition. These findings indicate that blood holds promise to identify epigenetic biomarkers that may be useful in stratifying neurological and psychiatric diseases, and as therapeutic targets, as they are in principle reversible.

Anti-TNFα restores disrupted metabolic interaction of the intestinal microbiome in IBD

SysINFLAME

Presenting Author: Ateequr Rehman

Ateequr Rehman(1),Konrad Aden(1,2), Silvio Waschina(3), Wei-Hung Pan(1), Alejandro Mena Nunez(1), Richa Bharti(1), Johannes Zimmerman(3) ,Johannes Bethge(2), Andre Franke(1), Susanna Nikolaus(2), Johann Oltmann Schroeder(2), Rainald Zeuner(2), Christoph Kaleta(3), Stefan Schreiber(1,2)), and Philip Rosenstiel(1)

(1) Institute of Clinical Molecular Biology, Christian-Albrechts-University and University Hospital Schleswig-Holstein, Campus Kiel, 24105 Kiel, Germany, (2) Department of Internal Medicine I., Christian-Albrechts-University and University Hospital Schleswig-Holstein, Campus Kiel, 24105 Kiel, Germany, (3) Institute for Experimental Medicine, Christian-Albrechts-University and University Hospital Schleswig-Holstein, Campus Kiel, 24105 Kiel, Germany

Biologics are an important treatment option for inflammatory bowel disease (IBD). Evidences suggests that the gut microbiota plays a critical role in the pathogenesis of IBD. However, the impact of biologic treatment on gut microbiota is poorly understood. In order to investigate the effect of biologic therapy on gut microbiota across inflammatory disorders, we tested the effect of anti-TNFα treatment between naive patients suffering from IBD or rheumatic disorders. To further investigate whether the impact of biologic therapy on gut microbiota depends on the therapeutic outcome (remission vs. non-remission) or the employed drug, we also analyzed set of biologic naïve IBD patients who were subjected to first-time anti-TNFα , anti- α4β7 or anti IL-6R antibody therapy. Both cohort underwent longitudinal stool sampling at determined time points before and after therapy induction. Gut microbiota was studied by 16S rRNA gene sequencing. Changes in microbiota before and after therapeutic interventions were assessed in terms of alpha and beta diversity, indicator species, and in-silico analysis of prediction of metabolic interactions. We observed that Intestinal microbial diversity and metabolic interaction among bacteria are decreased in both disease entities, IBD and RD. Biologic therapy is able to restore gut microbial diversity and metabolite exchange interactions among bacteria in IBD, but not RD. In contrast to microbial diversity, gut microbial metabolic interactions are specifically restored in IBD patients achieving clinical remission. This effect was independent of biologic treatment. In conclusion, we show that biologic therapy influences gut microbial diversity and metabolic interactions in IBD. In-silico metabolic interaction analysis is able to predict therapy response in patients with IBD under biologic treatment. Assessment of metabolic interactions of intestinal microbiota may serve as a marker for clinical response in IBD patients.

Multi-omics based strategy to predict graft function and personalize immunosuppressive therapy in kidney transplantation

e:Kid

Presenting Author: Nina Babel

Birgit Sawitzki1*, Chris Bauer2*, Nicole Wittenbrink3, Kerstin Wolk, Robert Sabat4, Harald Seitz5, Sven Olek6, Philipp Pagel7 Petra Reinke8, Christian Hugo9, Michal Or-Guil3, Nina Babel10

1Institute of Medical Immunology, Charité – Universitätsmedizin Berlin *both authors contributed equally 2MicroDiscovery GmbH, Berlin 3Systems Immunology Laboratory,Department of Biology, Humboldt University Berlin 4Interdisciplinary group Molecular Immunopathology, Charité-Universitätsmedizin Berlin 5 Fraunhofer Institute for Cell Therapy and Immunology, Branch Bioanalytics and Bioprocesses (IZI-BB), AG Biomarker Validation and Assay 6Epiontis GmbH, Berlin 7Numares GmbH, Regensburg 8Department of Nephrology and Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charité- Universitätsmedizin Berlin 9Division of Nephrology, University Hospital Dresden 10Medical Clinic I, Marien Hospital Herne, Ruhr University Bochum and BCRT, Charité-Universitätsmedizin Berlin

Achieving long-term transplant survival is an ultimate goal in transplant medicine. Early personalized therapy in patients at risk could prevent allograft loss and associated complications. However, there are no established markers predicting chronic allograft injury so far. Previous studies in renal transplant patients demonstrated that one-year renal graft function is an important predictor of transplant survival at ten-years post-transplant. Within the collaborative project e:KID we set out to establish a tool supporting risk prediction and personalized treatment of kidney transplant recipients that can be applied at early stage after transplantation and prevent chronic allograft injury. 596 renal transplant patients were included and monitored at eight different time points. We aimed to predict renal function at 12 months post-transplant based on marker analyses of earliest possible time point. Several omics technologies were applied to analyze markers from different regulation levels such as gene expression, protein expression, epigenetics, metabolites, cellular and clinical parameters. Uni- and multivariate linear regression were used to predict 1-year graft outcome using marker or marker combinations from different time points. To further evaluate the classification performance, we ran a resampling analysis by randomly sampling class assignment. Several single markers and marker combinations obtained already at week 2 post-transplant were able to predict 1-year graft function. While single parameter had a rather low predictive power, successive addition of more parameters (from one to finally four) increased the predictive value. Importantly, only the combination of markers from different regulation levels significantly improved the classification outcome. Taken together, our multi-omics data emphasize the importance of systems-medicine approach enabling risk prediction and personalized therapy in kidney transplant patients.

Keynote: Pharmacogenomics: from translational research to next generation benefit-risk evaluation

Presenting Author: Julia C. Stingl

Research division Federal Institute for Drugs and Medical Devices and University of Bonn

The molecular dimension of medicine that has developed during the last decades largely impacts our understanding of individual drug effects with respect to drug safety and efficacy. A new era of drug regulation has been opened by a deeper understanding of the variability in patients allowing stratified risk benefit evaluations. This involves the need for analysis of healthcare data together with pharmacogenomics or other –omics signatures for individualized treatment strategies.

Understanding pharmacogenomic variability between patients has impacted our understanding of variability in benefit-risk of drug effects. In drug metabolism, genetic polymorphisms affecting drug exposure lead to an increased risk in exposure-related side effects, but may as well lead to a change in response pattern due to variability in parent drug and metabolites. Therapy consequences of pharmacogenetic polymorphisms in drug metabolism may be genotype adjusted dosing or therapy modifications as proposed in several international evidence-based guidelines, or in the drug labels.

However, with the rapid development of genomewide and high-throughput data analysis methods, system medicine approaches and new biometric models for big-data evaluations enter the field of pharmacogenomics. For CYP2D6-genotype, successful prediction of the individual metabolizer group from large datasets of human brain imaging data was achieved by application of machine learning and boosting methods. In the era of digital health, longterm electronic health data together with imaging data and the patients' genome data will serve as basis for individualized and state-of-the-art healthcare. Pharmacogenomic data, if collected and protected adequately, will be used as companion diagnostics for therapy purpose. High performance computing clusters and NGS hubs dedicated specifically for companion diagnostics are needed to ensure best evidence based benefit-risk evaluations in precision medicine.

Integrating multi-omics and multi-modality medical imaging to assess hepatocellular carcinoma patient outcome under Sorafenib treatment: A progress report of the Multiscale HCC project

Multiscale HCC

Presenting Author: Mathew Divine

Sebastian Winkler, Erhan Kenar, Sven Fillinger, Wolfgang Thaiss, Johannes Schwenk, Matthias Kuthan, Franz Hilke, Michael Bitzer, Sven Nahnsen, Oliver Kohlbacher

Applied Bioinformatics, University of Tübingen, Tübingen, Germany; Quantitative Biology Center, University of Tübingen, Tübingen, Germany; Department of Radiology, University of Tübingen, Tübingen Germany; Department of Nuclear Medicine, University of Tübingen, Tübingen Germany; Department of Medical Genetics, University of Tübingen, Tübingen Germany; Department of Internal Medicine I, University of Tübingen, Tübingen Germany

The Multiscale HCC project is an observational clinical trial which includes patients that present with unresectable hepatocellular carcinoma (HCC) and are treated with Sorafenib, a multi-kinase inhibitor. Many patients do not respond to Sorafenib or develop resistance over the course of treatment. Due to the lack in understanding of resistance mechanisms, a multi-omics approach utilizing Next Generation Sequencing (NGS), Nuclear Magnetic Resonance (NMR) metabolite identification, and extensive multi-modality medical imaging has been undertaken to elucidate best practices for patient stratification and identification of therapy induced resistance. Patients receive a Dynamic Contrast Enhanced (DCE) Computed Tomography (CT) and two sets of combined Positron Emission Tomography and Magnetic Resonance Imaging (PET/MRI) scans that measure uptakes of [18F]FDG and [11C]Choline as well as multiple functional MRI sequences once before and up to two times after treatment start. At each time point biopsies are taken from tumor tissue, which is subjected to NGS, resulting in variant calling, RNAseq, methylation, and pharmacogenomic data sets. The multi-omics and medical imaging data are collected, pseudo-anonymized, and maintained on secure servers to which consortium partners have user defined access. To date, approximately 20 of 50 patients have been enrolled. Due to difficulties in obtaining and refining tumor tissue, there is currently an approximate 60% attrition rate for omics data collection. Multi-omics subnetworks have been identified, which show stark differences in refinement for responders compared to non-responders. Using a radiomics based approach for the medical imaging, we have been able to identify responders and non-responders based on baseline imaging using Linear Discriminant Analysis. Further work will investigate using multi-modality imaging to decrease the omics-attrition rate as well as tighter integration of –omics and imaging based technologies.

"Systems hematology" – Opportunities, benefits, and limitations

HaematoOPT

Presenting Author: Ingo Roeder

Ingmar Glauche, Christoph Baldow, Matthias Kuhn, Henrik Liebscher, Katja Hoffmann, Katja Tampe, Yuro Khefetz, Markus Loeffler, Markus Scholz

TU Dresden, Carl Gustav Carus Faculty of Medicine, Institute for Medical Informatics and Biometry , National Center for Tumor Diseases (NCT), Partner Site Dresden; University Leipzig, Faculty of Medicine, Institute for Medical Informatics, Statistics and Epidemiology

Systems medicine, i.e. the integration of theoretical/computational and clinical/experimental approaches, increasingly impacts basic, translational, but also clinical research. In particular, predictive mathematical models offer great potential to support clinical decision-making, e.g. with respect to treatment optimization. A particular challenge in this respect is provision and practical use of theoretical tools in clinical practice. To achieve acceptance and usability, math. models have to be integrated into routine procedures. We developed a systems-medical framework, which comprises the whole process from clinical data processing, over data analysis, to the generation of math. model predictions for individual patients. The framework is applied to two hematology-related use-cases: tyrosine kinase inhibitor treatment of chronic myeloid leukemia and chemotherapy of Non-Hodgkin lymphomas. It combines 3 layers: (i) a database solution, which guarantees a separation of patient identity data and pseudonymized clinical as well as simulation data, (ii) a web-server, which allows to access, allocate, and visualize data, and (iii) a model sever, which runs statistical analyses and generates mathematical predictions of disease dynamics for individual patients. The workflow has been constructed such that the user can access, visualize, and edit clinical data according to particular use-and-access rights via a web front-end. Additionally, it allows to request and present statistical analyses and model-predictions of disease kinetics under different treatment scenarios. Based on the model predictions the effect of a particular treatment (adaptation) can be evaluated prospectively. The implemented framework demonstrates how systems medicine can practically support the daily routine in the clinic. Although applied to two specific examples from hematology, the frameworks itself is neither restricted to particular disease scenarios nor to particular mathematical models.

How to report somatic variants in molecular tumor boards

Genoperspektiv

Presenting Author: Tim Beißbarth

Júlia Perera-Bel1, Barbara Hutter2, Christoph Heining3, Annalen Bleckmann1, Martina Fröhlich2, Stefan Fröhling3,4, Hanno Glimm3,4, Benedikt Brors2 and Tim Beißbarth1

1University Medical Center Göttingen, 2German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), 3National Center for Tumor Diseases (NCT) and German Cancer Research Center (DKFZ), 4German Cancer Consortium (DKTK)

The understanding of complex diseases, such as cancer, has furthered with the improvements of high-throughput technologies e.g., next-generation sequencing. However, advances in technology platforms and bioinformatic tools contrast with the scarce implementation of cancer genomics in clinical practice. One reason for this situation is that pathologists and oncologists have to face thousands of genomic alterations and unravel their clinical relevance. Accordingly, the scientific community has claimed the need of a comprehensive knowledge database as well as decision support platforms for the interpretation and reporting of genomic findings in clinical practice e.g., in molecular tumor boards. Towards this end, we have developed a framework for interpreting and reporting genomic data relying entirely on public knowledge. The method focuses on actionable variants - genomic alterations that predict drug response. In particular, gene-drug associations are classified according the stage of development of the drug (approved, clinical trials or pre-clinical studies) and the cancer type for which the predictive association exists. We tested the framework on the Pan-Cancer dataset from The Cancer Genome Atlas (3184 samples from 12 cancer types) and 11 patients from the NCT MASTER trial – whose treatment decisions where based on genomic data. We showed that the reporting method is able to 1) find actionable variants in the majority of the patients and, 2) reproduce experts' treatment suggestions in the MASTER dataset. We present a proof-of-concept for a method to report treatment options based on the genomic profile of the patient. It is designed as a supporting tool for all clinicians, biologists and bioinformaticians working with genomic characterization of patients in clinical routine and facing complex decisions regarding treatment options.

Poster Presentations

Flash Talks

Poster Session I – Odd numbers

Poster Flash Talks I: Tuesday, November 21, 04.30 – 05.00 pm

Poster Exhibition I: Tuesday, November 21, 05.00 – 06.30 pm

Poster Session II – Even numbers

Poster Flash Talks II: Wednesday, November 22, 05.00 – 05.30 pm

Poster Exhibition II: Wednesday, November 22, 05.30 – 07.00 pm

Poster Session I – Odd numbers: Tuesday, November 21, 04.30 – 05.00 pm				
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129	P 1	Matthias Ganzinger	Long-Term Conservation of Bioinformatics Pipelines for Systems Medicine	CLIOMMICS
131	P 3	Florian Auer	ndexr – an R package to interface with the Network Data Exchange	MMML-Demonstrators, MultiPath
133	P 5	Raik Otto	Comparing characteristic genomic variants allows reliable in-silico identification of Next-Generation sequenced Cancer Cell Line samples	MAPTor-NET
209	P 75	Zaynab Hammoud	Implementing a multilayer framework for pathway data integration, analysis and visualization	MultiPath
235	P 101	Stefan Albert	A hierarchical stochastic model for bistable perception	PsychoSys
223	P 89	Ines Assum	Establishment of Multi-OMICs Pathway Analysis in Human Atrial Fibrillation	symAtrial
176	P 45	A.C. Hansson	Oxytocin reduces alcohol cue-reactivity in alcohol dependent rats and humans	SysMed-Alcoholism
152	P 21	I. Haffner	Central validation of HER2 status to determine heterogeneity of marker expression in HER2 positive gastric cancer (GC)	SYS-Stomach
247	P 109	Maciej Rosolowski	Longitudinal analysis of cytokine profiles in community-acquired pneumonia	CAPSyS
249	P 111	Ellen Witte	Cytokine X* is a component of a pathway leading to allograft damage and an early indicator of poor graft function in patients after kidney transplantation (* Patent application in preparation)	e:Kid

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155	P 24	H. Hatzikirou	Harnessing the predictive potential of tumor heterogeneity via the integration of MALDI imaging data and dynamic modeling	SYSIMIT
252	P 114	Tracy Erwin-Grabner	Pre-mapping Networks for Brain Stimulation (PreNeSt)	PreNeSt
135	P 8	Ulrik Stervbo	BKV clearance time correlates with the exhaustion state and T-cell receptor repertoire shape of BKV-specific T-cells in renal transplant patients with severe BKV infection	e:Kid
183	P 52	Anna Maaser	Exome sequencing of multiply affected bipolar disorder families and follow-up resequencing implicate rare variants in neuronal genes contributing to disease etiology	IntegraMent
236	P 102	Julia C Fitzgerald	Metformin reverses TRAP1 mutation-associated alterations in mitochondrial function in Parkinson's disease	Mito-PD
159	P 28	Robert Häsler	Inflammatory bowel disease progression is associated to epigenetic regulators and their target genes	SysINFLAME
169	P 38	Baiba Vilne	Genetic determinants of aberrant splicing events in coronary artery disease	e:Athero-Sysmed
196	P 62	Alexandra Poos	Using Mixed Integer Linear Programming to identify regulators of telomerase expression	CancerTelSys
187	P 56	Urs Heilbronner	Common genetic variants associated with personality dimensions in the Heidelberg Cohort Study of the Elderly (HeiDE): an update	IntegraMent

Poster Presentations

Overview

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Poster Exhibition I: Tuesday, November 21, 05.00 – 06.30 pm

Poster Session II – Even numbers
Poster Flash Talks II: Wednesday, November 22, 05.00 – 05.30 pm
Poster Exhibition II: Wednesday, November 22, 05.30 – 07.00 pm

Technologies in Systems Medicine				
Page	**Posterno.**	**Presenting Author**	**Poster Title**	**e:Med associations**
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130	P 2	Volker Daum	Deep Learning for the Prediction of Treatment Response to Sorafenib in Patients with Hepatocellular Carcinoma	Multiscale HCC
131	P 3 - FT	Florian Auer	ndexr – an R package to interface with the Network Data Exchange	MMML-Demonstrators, MultiPath
132	P 4	Florian Auer	Bringing Pathway Knowledge to Systems Medicine Approaches	MMML-Demonstrators, MultiPath
133	P 5 - FT	Raik Otto	Comparing characteristic genomic variants allows reliable in-silico identification of Next-Generation sequenced Cancer Cell Line samples	MAPTor-NET
134	P 7	Nadine Sarah Schaadt	Mathematical Approach to determine the Degree of Lymphocytic Organization in Immune Cell Infiltrates	SYSIMIT
135	P 8 - FT	Ulrik Stervbo	BKV clearance time correlates with the exhaustion state and T-cell receptor repertoire shape of BKV-specific T-cells in renal transplant patients with severe BKV infection	e:Kid
136	P 9	Björn Samans	Development of a tool to predict renal graft rejection based on a novel epigenetic qPCR	e:Kid
137	P 10	Cornelius Knopp	Research data management with openBIS: A validatable data management solution for a multi-center e:Med consortia	SysINFLAME
138	P 11	Maria Fedorova	(ox)Lipidomics data acquisition and integration for systems medicine view on metabolic disorders	SysMedOs
139	P 12	Zhixu Ni	High-throughput identification of native and oxidized phospholipids from LC-MS and shotgun lipidomics datasets to assist biomarker discovery in metabolic diseases	SysMedOs
140	P 13	Wiebke Sick	Standardization in Systems Medicine	ModMen

Poster Flash Talk marked by FT

Systems Medicine of Diseases				
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145	P 14	Mirjam Figaschewski	Method development for the integration of multi-omics data using a preclinical mouse model	Multiscale HCC
146	P 15	Stefan Kallenberger	Paradoxical amplification of MAPK and PI3K/Akt signaling activities due to overexpression of CBL ubiquitin ligases	PANC-STRAT
147	P 16	Kerstin Schönbeck	Neuroblastoma tumor progression is favored by Hippo-YAP pathway activation	SMOOSE, SYSMED-NB
148	P 17	Karin Schmelz	Intratumoral Heterogeneity in Neuroblastoma defined by Multiregion Sequencing	SYSMED-NB
149	P 18	Johannes Brägelmann	Screening 1505 kinase inhibitors across lung cancer cell lines reveals CDK9 as a synthetic lethal target in NUT midline carcinoma	MILES
150	P 19	Carina Lorenz	Investigation of Drug Tolerant Persister Cells in EGFR-mutated lung adenocarcinoma	MILES
151	P 20	Gwen Zwingenberger	Effects of trastuzumab and afatinib on kinase activity in gastric cancer cell lines	SYS-Stomach
152	P 21 - FT	I. Haffner	Central validation of HER2 status to determine heterogeneity of marker expression in HER2 positive gastric cancer	SYS-Stomach
153	P 22	A. Arlt	Hodgkin lymphoma cells trigger in vitro differentiation of human monocytes into macrophages of the M2-subtype	MMML-Demonstrators
154	P 23	Michael Altenbuchinger	Molecular signatures that can be transferred across different omics platforms	MMML-Demonstrators
155	P 24 - FT	H. Hatzikirou	Harnessing the predictive potential of tumor heterogeneity via the integration of MALDI imaging data and dynamic modeling	SYSIMIT
156	P 25	Martin Siegemund	Synergistic co-treatment and targeting of tumor-associated antigens increase the apoptotic activity of TRAIL fusion proteins on melanoma cells	Melanoma sensitivity
157	P 26	Peter Ahnert	Sequential Organ Failure Assessment (SOFA) Score as Operationalization of Disease Severity of hospitalized Community acquired Pneumonia (CAP)	CAPSyS
158	P 27	Bernd Schmeck	Macrophages render lung epithelial cells hypo-responsive to Legionella pneumophila – a systems biology study	CAPSyS
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163	P 32	Kristina Schlicht, Carolin Knecht	Investigation of the genetic architecture of metabolic coherence	SysINFLAME
164	P 33	Marie Tempel	Measurement of calprotectin in an IBD kindred cohort in Germany	SysINFLAME
165	P 34	Theresa Schlegel	Systems diagnostic of the human gut microbiome on inflammatory diseases using metaproteome analysis of fecal samples	
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167	P 36	Georgia Angelidou	Reconstructing lipid peroxidation products (LPPs) metabolic networks for systems medicine view on obesity and type II diabetes.	SysMedOs
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169	P 38 - FT	Baiba Vilne	Genetic determinants of aberrant splicing events in coronary artery disease	e:AtheroSysmed
170	P 39	Helena U. Zacharias	Associations between mental health, type-2 diabetes mellitus incidence, and human serum metabolome revealed by mixed graphical models	e:AtheroSysmed
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172	P 41	Enrico Glaab	In silico analysis of candidate drug targets in the alpha-synuclein regulatory network	Mito-PD
173	P 42	Christian Johannes Gloeckner	Data-independent acquisition analysis of the mitochondrial proteome to identify quantitative, disease-specific signatures	Mito-PD
174	P 43	Daniela Vogt Weisenhorn	Behavioral alterations in the Pink1-Q126P mouse model	Mito-PD
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178	P 47	Georg Köhr	Patterns of prefrontal cell firing during extinction learning and recall of alcohol-related memories in rats	SysMed-Alcoholism
179	P 48	Jerome Clifford Foo	Characterizing response and non-response to therapeutic sleep deprivation: clinical and genetic factors	IntegraMent, SysMed-Alcoholism
180	P 49	Josef Frank	Support for Contribution of Genetic Risk for Major Depressive Disorder to Alcohol Dependence	IntegraMent, SysMed-Alcoholism
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182	P 51	Lalit Kaurani	Early life stress in Schizophrenia: The role of microRNAs	IntegraMent
183	P 52 - FT	Anna Maaser	Exome sequencing of multiply affected bipolar disorder families and follow-up resequencing implicate rare variants in neuronal genes contributing to disease etiology	IntegraMent
184	P 53	Anna C. Koller	Exome sequencing in multiply affected families identifies new candidate genes for schizophrenia	IntegraMent
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187	P 56 - FT	Urs Heilbronner	Common genetic variants associated with personality dimensions in the Heidelberg Cohort Study of the Elderly (HeiDE): an update	IntegraMent
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207	P 73	D. Kube	Synergistic changes in global gene expression and cellular metabolism by factors of the microenvironment.	MMML-Demonstrators
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215	P 81	Sibylle Schirm	A Biomathematical Model of Immune Response and Treatment in Mice with Pneumococcal Lung Infection	CAPSyS
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e:Med
SYSTEMS MEDICINE

Poster Presentations

Technologies in Systems Medicine

Long-Term Conservation of Bioinformatics Pipelines for Systems Medicine

CLIOMMICS

Presenting Author: Matthias Ganzinger

Blanca Flores (a), Dirk Hose (b), Anja Seckinger (b), Petra Knaup (a), Matthias Ganzinger (a)

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(b) Department of Internal Medicine, Heidelberg University Hospital, Heidelberg, Germany

Introduction Sequencing and analysis of genomic data has become a valuable technology in both research and clinical settings. Typically, bioinformatics facilities develop and maintain their own chain of analytical steps, the analytical pipeline. For each step, researchers can choose from a variety of computer programs. Unfortunately, newer versions of components can lead to unintended side effects that may cause different results. The problem of varying pipeline components is intensified by modular software like R, where packages have update cycles independent of the main software. In clinical as well as research use reproducibility of pipeline results is of great importance. Consequently, technical and organizational steps are necessary to manage documentation, ensure version control and validate pipeline configurations. Methods To mitigate problems resulting from diverging software versions, we have developed a snapshot-based concept for conserving pipelines. Snapshots can be compared to freezing the whole runtime environment including all software components as they are installed at the time of taking the snapshot. The snapshot can be reactivated later or be transferred to another environment to replicate the pipeline. Results For CLIOMMICS, we implemented a pipeline for automatically generating reports for sequencing data. Docker containers (https://www.docker.com/) are used for pipeline steps relying on R. In these containers, the complete set of dependent R packages is maintained to ensure reproducibility and portability to other computers. In addition to Docker, we use KNIME (https://www.knime.com/) for managing the pipeline. Discussion Our snapshot approach worked well for CLIOMMICS to conserve complex pipeline configurations. However, snapshots can make the impression of a black box, where it is hard to understand what happens inside. Thus, carefully documenting the pipeline functionality is an important additional step.

Deep Learning for the Prediction of Treatment Response to Sorafenib in Patients with Hepatocellular Carcinoma

Multiscale HCC

Presenting Author: Volker Daum

Volker Daum, Julia Gawellek, Dieter Hahn, Marcus Prümmer

Chimaera GmbH

Current clinical practice generates a high amount of multi-modal imaging data for diagnosis and treatment monitoring of cancer. This data is generally only analyzed for changes in tumor growth and proliferation. However, the application of texture analysis methods has already shown that imaging data can contain more information than is visible to the human eye. We aim to extract this information by the application of texture features and Convolutional Deep Neural Networks to multi-modal imaging data (CT, VPCT, PET, MRT). As a prerequisite, all multi-modal imaging data is spatially aligned by rigid and non-rigid registration in a common frame of reference. To generate more individual samples from the available patient data we apply machine learning methods on 2D image patches. The patches are extracted as sub-regions from multi-modal images of the individual patients and show tumor tissue. Finally, we apply texture analysis and Deep Neural Networks to find correlations between the extracted features and a classification of the patients' treatment response into three categories: "responder", "non-responder" and "stable disease". The methodology is applied to predict the likelihood of treatment response to Sorafenib in patients with Hepatocellular Carcinoma (HCC) based on a baseline image acquisition. The images are acquired in the scope of the observational clinical study that is performed in the e:Med funded project "Multiscale HCC". The acquisition protocol is standardized such that for each patient the same imaging data in terms of modalities and imaging parameters is available. This approach helps to minimize variation in the data that is not related to the patient. Currently, 13 patients in the study are available for evaluation of early results of this approach. On this pool of data, the first results already indicate that the approach can discriminate between "responder" and "non-responder".

ndexr – an R package to interface with the Network Data Exchange

MMML-Demonstrators, MultiPath

Presenting Author: Florian Auer

Florian Auer, Zaynab Hammoud, Alexandr Ishkin, Dexter Pratt, Trey Ideker and Frank Kramer

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Motivation: Seamless exchange of biological network data enables bioinformatic algorithms to integrate networks as prior knowledge input as well as to document resulting network output. However, the interoperability between pathway databases and various methods and platforms for analysis is currently lacking. NDEx, the Network Data Exchange, is an open-source data commons that facilitates the user-centered sharing and publication of networks of many types and formats. Results: Here, we present a software package that allows users to programmatically connect to and interface with NDEx servers from within R. The network repository can be searched and networks can be retrieved and converted into igraph-compatible objects. These networks can be modified and extended within R and uploaded back to the NDEx servers. Availability: ndexr is a free and open-source R package, available via GitHub https://github.com/frankkramer-lab/ndexr and Bioconductor http://bioconductor.org/packages/ndexr/

Bringing Pathway Knowledge to Systems Medicine Approaches

MMML-Demonstrators, MultiPath

Presenting Author: Florian Auer

Florian Auer, Tim Beißbarth and Frank Kramer

Department of Medical Statistics, University Medical Center Göttingen

In modern Systems Medicine approaches the aim is to look at increasingly complex interactions of complete signaling pathways in order to get a more holistic view for individualized treatment decisions. Individualized treatment decisions and newly developed specialized drugs warrant the need to broaden the focus in individualized medicine from singular biomarkers to pathways. On the other hand pathway databases offer vast amounts of knowledge on biological networks, freely available and encoded in semi-structured formats[BCS06, SAK+09]. The efficient re-use of pathway knowledge and its integration into bioinformatic analyses enables new insights for researchers in systems medicine. However, the vast amount of published data on molecular interactions makes it increasingly challenging for life science researchers to find and extract the most relevant information. Currently, the tools to use this information and integrate it in a clinical context are still lacking. Our idea is to compose an analysis pipeline in order to enable patient-specific systems medicine analyses in a university hospital setting. Our poster will present a workflow for visualizing pathway information and integrating omics data within an interactive online application, utilizing state of the art technology[FLH+16, R C14, KBK+ 13, FBBL15] and well-established standard data models[DCP+ 10, HFS+ 03, PCW+ 15].

Comparing characteristic genomic variants allows reliable in-silico identification of Next-Generation sequenced Cancer Cell Line samples

MAPTor-NET

Presenting Author: Raik Otto

Raik Otto, Christine Sers, Ulf Leser

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Cancer cell lines are a pivotal tool for cancer researchers. However, cancer cell lines are prone to critical errors such as misidentification and cross-contamination which have reportedly caused severe setbacks. Established cancer cell line identification methods compare genotype characteristics obtained during specific experiments (e.g. SNP arrays); characteristic genotype properties of the to-be-identified sample (the query) are matched against the same characteristics properties of the known samples (the references). If a match shows a significant similarity to a reference sample, the query is identified as the reference sample. Such characteristic genotype information can also be derived from NGS data. A query can be identified when the characteristic genotype properties were obtained from Next-generation sequencing of the query and a subsequent comparison to a NGS reference. However, results from different NGS technologies, algorithms and sequencing-approaches, e.g. whole-exome or panel-sequencing, are inherently challenging to compare. SNP-zygosity matching and tandem repeat-counting on such data is in general unreliable due to non-covered loci, SNP-filtering, and zygosity-call divergence caused by differing algorithmic ploidy-settings. Here, we present the Uniquorn method that reliably identifies cancer cell line samples based on NGS genotyping data across different technologies, algorithms, filter-settings and covered loci. Uniquorn compares the query to all references and computes a p-value for the likelihood that an overlap in observed genomic variants is due to chance. Uniquorn was benchmark by cross-identifying 1989 cancer cell line sequencing samples: sensitivity amounted to 96% and specificity to 99%. The R-BioConductor package Uniquorn and the benchmark setup are freely available.

Mathematical Approach to determine the Degree of Lymphocytic Organization in Immune Cell Infiltrates

SYSIMIT

Presenting Author: Nadine Sarah Schaadt

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(1) Institute for Pathology, Hannover Medical School, Germany, (2) Definiens AG, Munich, Germany, (3) Nephrology, Hannover Medical School, Germany

Many inflammatory conditions are characterized by invasion of circulating immune cells into tissues. This is referred to as “immune cell infiltrate” and described by semi-quantitative terms („focal“/“diffuse“) or by their relation to specific compartments (e.g. „perivascular“). Our motivation is to formalize the evaluation of infiltrates, enabling a standardized assessment and integration into mathematical modeling of immune cells in their spatial context. We apply this approach to evaluate the formation of tertiary lymphoid organs (TLOs), a process that starts with accumulation of B-cells at sites of chronic inflammation. TLOs are relevant beyond a specific disease. Thus, we demonstrate the disease-overarching value of the approach in onco-immunology and transplantation medicine. Our workflow includes a graph-based description of immune infiltrates at cellular level in digital whole slide images using CD3/CD20 duplex staining. This first step identifies infiltrates, which are classified according their specific structures in a second step. For this, the clustering behavior and a consideration of minimal cut-sets and features representing the heterogeneity are combined to estimate the degree of spatial organization. An application compares samples of renal transplantations, breast cancer, and lung tissue from cystic fibrosis patients. We characterized the composition of infiltrates in an observer-independent, reproducible way and categorized them based on their degree of commonality with mature TLOs. For this, we propose new categories of early (“unstructured”, “intermediately organized”) and later (“TLO-like”) stages of B- and T-cell compartmentalization. The identified structures showed a high similarity between different diseases. A formalized description allows the transfer between imaging data and dynamical behavior simulated by mathematical modeling and has high potential for application in clinically relevant immune cell evaluation.

BKV clearance time correlates with the exhaustion state and T-cell receptor repertoire shape of BKV-specific T-cells in renal transplant patients with severe BKV infection

e:Kid

Presenting Author: Ulrik Stervbo

Ulrik Stervbo, Mikalai Nienen, Benjamin JD Weist, Leon Kuchenbecker, Patrizia Wehler, Timm H Westhoff, Petra Reinke, Hans-Dieter Volk, and Nina Babel

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Reactivation of the BK polyomavirus is known to lead to severe complications in kidney transplant patients. The current treatment strategy relies on decreasing the immunosuppression to allow the immune system to clear the virus. Recently we demonstrated a clear association between the resolution of BKV reactivation and reconstitution of BKV-specific CD4+ T-cells. However, the factors determining the duration of the clearance of the viral infection remain unknown. Here we apply a combination of in-depth multiparametric flow cytometry and CDR3 beta chain receptor repertoire analysis of BKV specific T-cells to a cohort of 5 kidney transplant patients with BKV reactivation. In this manner we were able to track the TCR repertoires at single clone levels during the clinical course of BKV infection. The number of BKV-specific T-cells in peripheral blood did not affect the duration of BKV infection. In contrast, the diversity of the T-cell receptor repertoire as well as exhaustion status of BKV-specific T-cells correlated with the duration of viral clearance. This duration was further found to be independent of hyperexpanded, immunodominant BKV-specific T-cell clones and of the overall magnitude of cellular immunity. Rather, the diversity of BKV-specific TCR repertoire in peripheral blood: high diversity of the repertoire and lack of PD1 and TIM-3 exhaustion markers on BKV-specific T-cells is associated with short remission time. Our data demonstrate that the quality (exhaustion status and shape of the repertoire) rather than quantity of BKV-specific T-cells determines the remission time after BKV reactivation.

Development of a tool to predict renal graft rejection based on a novel epigenetic qPCR

e:Kid

Presenting Author: Björn Samans

B. Samans, K. Schildknecht, M. Or-Guil, N. Babel and S. Olek

Epiontis GmbH, Berlin, Department of Nephrology, Charité, Berlin, Germany

No biomarkers for timely and accurate prediction of graft rejection upon kidney transplantation are known. Here, an epigenetic qPCR assay for kidney-specific proximal tubular epithelial cells (pTECs) is described and its value as rejection marker was determined in urine, blood or serum. A critical adverse event upon kidney transplantation is rejection of the donor organ. Immunosuppressive therapy is used prevent this process, but is insufficient often resulting in viral reactivation and/or failure to prevent rejection. Current diagnostic methods to identify such complications are invasive and mostly not timely to support better therapeutic interventions. Novel biomarkers could increase the graft survival and patient life quality. Here, we present an epigenetic assay for pTecs potentially allowing an early detection of increased shedding of pTEC DNA in urine or blood. Such increase may indicate an early manifestation of rejection. Methylation patterns in a defined gene region of target cells (pTECs) and control cells (. urothelial cells (HUC), glomerular endothelial cells (GEC) and leukocyte subpopulations were analysed by bisulfite sequencing. Upon identifying a PTEC specific demethylated region, a qPCR assay was designed. The assay performance is assessed by specifity, selectivity and sensitivity showing high accuracy in detecting pTECs in urine samples. Demethylation based quantification of PTECs in different specimens by epigenetic qPCR assay to monitor patients after kidney transplantation for adverse events seems to be a possible alternative to improve screening. Next, the assay has to be validated and tested in a case-control study.

Research data management with openBIS: A validatable data management solution for a multi-center e:Med consortia

SysINFLAME

Presenting Author: Cornelius Knopp

Cornelius Knopp, Christian R Bauer, Ulrich Sax

University Medical Center Göttingen

One of the fundamental issues in supporting medical research is data management in its basic form: the maintenance of files. Many research projects still store raw, result and analysis files on local hard drives without traceable versioning, metadata information and access management. This is not only troublesome during the active research progress, but even more when research should be reproducible, auditable and ready for long-term archiving. A solution to this problem are research management systems with file storage capability. The openBIS platform is an open source research management system by the CISD group of ETH Zurich. It was developed with the goal to support biological research data workflows. The multi-center consortium sysINFLAME is investigating inflammatory diseases. With many different source systems, data types and researcher collaborating on all stages of data creating workflows in different institutes, we aimed at providing a robust and useful research management framework. One example for the necessity of research data management tools is the utilization of microbiome data in sysINFLAME. The workflow starts with the extraction of bacterial genes from stool samples, data-cleaning and ends with identifying the amount of bacteria genera and cumulative analyses. We examined the data files originating at each step and chose relevant metadata to develop a research supporting platform. The regular openBIS configuration allows for (1) checking in, (2) versioning, (3) deriving analysis data from the raw data, (4) storing the process steps. All data is linked to reproduce traceable data to information flows. Researchers can store and retrieve data via a web GUI with individual metadata forms and access to the data depending on the researcher's role. Aiding the research process by researchers spread over all stages, openBIS's additional value in providing a basis for unified data access and long-term archiving have to be investigated next.

(ox)Lipidomics data acquisition and integration for systems medicine view on metabolic disorders

SysMedOs

Presenting Author: Maria Fedorova

(ox)Lipidomics data acquisition and integration for systems medicine view on metabolic disorders

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Human lipidome consists of a large number of structurally and functionally diverse species characterized by a wide dynamic range of cellular and tissue concentrations. Lipids do not only serve as an energy depot and building blocks of biological membranes, but also play a significant role in regulating metabolic pathways and cell signaling. To uncover diversity of lipid species and understand their functional roles in human pathophysiology it is important to have access to high-throughput technology platforms for lipidome analysis. However, in comparison to highly advanced Omics techniques such as genomics, transcriptomics and proteomics, lipidomics is relatively less developed. Moreover, dynamic modifications of lipids via enzymatic and non-enzymatic oxidation, shown to play a detrimental role in numerous human diseases, are not usually studied in Omics way. To address the variety of native and modified lipids in biological samples we developed LC-MS based (ox)Lipidomics analytical platform which allows us to target unoxidized and differentially modified lipid species. To facilitate high-throughput workflows several software tools were developed for lipid (LipidHunter) and oxidized lipid (LPPtiger) identification. Finally, experimental and publicly available information on oxidized lipids is integrated via knowledge database LPPdb. This multi-level lipidomics approach is currently applied to clinical samples (blood plasma and adipose tissue) from patients with obesity and type II diabetes. Overall, (ox)Lipidomics platform provides high-throughput solutions for data acquisition and integration on lipid dynamics and modifications required for systems medicine view on human pathogenesis.

High-throughput identification of native and oxidized phospholipids from LC-MS and shotgun lipidomics datasets to assist biomarker discovery in metabolic diseases

SysMedOs

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Lipids are generally acknowledged as a dynamic constituent of biological systems capable to react and reflect any changes in physiological states. Thus, there is a large interest in lipid-derived markers for diagnostic and prognostic applications, especially in translational and systems medicine research. However, high-throughput lipid identification remains a bottle-neck of modern untargeted lipidomics. We developed two new open source software for the high-throughput identification of phospholipids in data-dependent LC-MS and shotgun datasets: LipidHunter for normal phospholipids (PLs) and LPPtiger for oxidized phospholipids (oxPLs). LipidHunter provides an easy and efficient way of PL identification by resembling a workflow of manual spectra annotation. Lipid identification is based on MS/MS data analysis in accordance with defined fragmentation rules for each PL class. LPPtiger uses PLs identified by LipidHunter to predict and identify oxPLs from the same dataset. The relative quantification of identified PLs and oxPLs allows the monitoring of dynamic reconfiguration of the cellular lipidome in response to mild nitroxidative stress. LipidHunter and LPPtiger are freely available as source code and Windows executable distributions at https://bitbucket.org/SysMedOs.

Standardization in Systems Medicine

ModMen

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In systems medicine, high-throughput technologies produce large amounts of data on different biological processes, including (disturbed) gene expressions, metabolic pathways and signaling. The large volume of different types of data, stored in separate databases and often located at different geographical sites, has posed new challenges regarding processing, integration, and representation of these data. Hence, numerous bioinformatics tools have been developed to resolve these upcoming problems. In this context a great deal of attention has been focussed on the standardizing of data and processes, primarily to retrieve and to combine large, heterogeneous packages of information into standardized datasets. This data-centred concept of standardization in systems medicine, however, is in contrast to the debate on standardization in the social studies of science and technology that rather emphasizes the dynamics, contexts and negotiations of standard setting processes. Based on interviews done with researchers belonging to research consortia that explore the molecular basis of diseases in order to establish clinical systems medicine approaches in Germany, we trace how data are standardized and shaped by standardizing procedures and bioinformatics tools. Furthermore, we explored how scientists utilizing such data in research perceive standards and standard setting procedures, and which consequences for knowledge production (e.g. modeling) arise from standardizations. Different concepts and meanings of standardization are explored to get a deeper insight into practices and procedures that are increasingly important for knowledge generation not only in systems medicine, but also beyond.

Poster Presentations

Systems Medicine of Diseases

Method development for the integration of multi-omics data using a preclinical mouse model

Multiscale HCC

Presenting Author: Mirjam Figaschewski

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The multikinase inhibitor Sorafenib is used routinely in the treatment of unresectable hepatocellular carcinoma (HCC), and patients often do not respond to or develop resistance to Sorafenib. Due to the limited knowledge of resistance mechanisms, we have developed a preclinical, multi-omics approach, utilizing translational proteomics and medical imaging technologies to understand the underpinnings of resistance. We genetically modified two sets of C57BL/6 mice to develop HCC, which were induced by means of hydrodynamic injection to create CaMIN (c-Myc + NRasG12V) or CaMIA (c-Myc + Akt-1) gene alterations. The mice were then divided into two groups each: control and sorafenib treated. Mice were subsequently measured once weekly over a three week period with various Positron Emission Tomography (PET) tracers to determine the best imaging biomarker for Sorafenib resistance development: [18F]FDG: glucose metabolism, [18F]FLT: proliferation, [68Ga]-NODAGA-RGD: angiogenesis, [18F]FMISO: hypoxia. After the final imaging procedure, proteomics data was generated from tumor tissue using a high-resolution Orbitrap Velos instrument, resulting in over 3500 quantified protein expression values. Regions of interest were drawn over tumors in the imaging data, and further processed, which resulted in 76 quantitative radiomics features describing each tumor. Radiomics features were reduced to 18 using a wilcoxon non-parametric test, and clustering revealed two distinct phenotypes, which were separable using spectral clustering and a Gaussian Mixture Model. A Principle Component Analysis of protein expression values revealed separation of groups based on imaging tracer, suggesting these values to be highly susceptible to differences in anesthesia and fasting protocols during imaging experiments. Thus, our multi-omics approach reveals that the proteome is altered by imaging protocols, possibly affecting the validity of imaging experiments, requiring finely tuned protocols.

Paradoxical amplification of MAPK and PI3K/Akt signaling activities due to overexpression of CBL ubiquitin ligases

PANC-STRAT

Presenting Author: Stefan Kallenberger

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Dysregulation of signaling pathways is known to be one of the major causes of cancer development. Pancreatic ductal adenocarcinoma (PDAC) is one of most malignant cancer types. Chemotherapy in PDAC mostly fails from acquired resistance of tumor cells. By experiments and mathematical modeling, we investigated the role of casitas B-lineage lymphoma (CBL) ubiquitin ligases that are negative regulators of receptor tyrosine kinases (RTKs) and are often downregulated in tumors. It is well established that CBL ubiquitin ligases negatively regulate active RTKs by targeting them for degradation or accelerating their removal from the cell surface. Interestingly, we observed a paradoxical amplification of MAPK and PI3K/Akt signaling activities in PDAC cells overexpressing a CBL ubiquitin ligase that were treated by the TKI inhibitor erlotinib. To understand this phenomenon and test possible mechanistic hypotheses, we created an ODE model describing epidermal growth factor receptor (EGFR) signaling, MAPK and PI3K/Akt pathways. Immunoblot data of PDAC cells exposed to erlotinib and/or EGF were used for model calibration. Assuming that CBL ubiquitin ligases increase the signal transduction from active EGFR complexes by acting as scaffolds for mediators of downstream kinase signaling, the model could explain the experimentally observed effect of an increased Erk and Akt activation in presence of erlotinib. Taken together, we could characterize a new significant role of CBL ubiquitin ligases in PDAC cells. Whereas, CBL enzymes were described as inhibitors of RTK signaling, they apparently serve as activators of MAPK and PI3K/Akt pathways on a short timescale, which can be explained by their function as signal amplifying scaffolds at EGFR complexes.

Neuroblastoma tumor progression is favored by Hippo-YAP pathway activation

SMOOSE, SYSMED-NB

Presenting Author: Kerstin Schönbeck

Kerstin Schönbeck*, Melanie Witthauer*, Annika Winkler*, Annabell Szymansky*, Falk Hertwig*, Joern Toedling*, Alexander Schramm#, Angelika Eggert*, Johannes H. Schulte*

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Neuroblastoma is a solid tumor of childhood originating from neural crest progenitors. While neuroblastomas predominantly arise in the adrenal glands and the abdomen, metastases can also occur in organs such as liver, bone marrow and pancreas. Tumor relapses occur in about 50% of high-risk neuroblastoma patients, and treatment of highly metastatic high-risk neuroblastoma is still a major clinical challenge. By analyzing triplets of neuroblastoma patients, comprising primary tumors, relapse samples and blood, WGS and RNA-sequencing revealed a relapse-specific pattern of Hippo-YAP pathway activation. As YAP1 is a well-known oncogene in many other tumor entities, such as lung, liver and ovarian cancer, we investigated YAP1 protein- and mRNA levels in 19 neuroblastoma cell lines. YAP1 was found to be variably expressed in the set of cell lines, which originate from various primary and metastatic tumor sites. We next investigated the functional role of YAP1 in neuroblastoma. Cell viability and proliferation rates were found to be significantly decreased in a number of neuroblastoma cell lines upon YAP1 knockdown. Moreover, overexpression of constitutively active YAP1(S127A) revealed a metabolism-regulating role of YAP1 in neuroblastoma. Hippo-YAP activated cells showed a higher glucose uptake and an increased lactate production than empty-vector control cells. Also, YAP1 activated cells were able to overcome the growth inhibition induced by serum starvation, in contrast to empty-vector controls. (Contrary to our expectations cell motility was found not to be affected upon induction or inhibition of YAP1 in vitro.) Next, we aim to characterize the role of the Hippo-YAP pathway in the metabolic adaption of neuroblastoma cells in response to stress factors such as limited nutrient supply. Furthermore, we seek to investigate a possible contribution of the Hippo-YAP pathway to aerobic glycolysis, also known as 'Warburg Effect'.

Intratumoral Heterogeneity in Neuroblastoma defined by Multiregion Sequencing

SYSMED-NB

Presenting Author: Karin Schmelz

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Neuroblastoma (NB) is a common childhood tumor that arises from the neural crest and shares ancestor cells with the sympathetic nerve system. Neuroblastoma comprises a heterogenous disease with a subset of tumors undergoing spontanous regression while nearly 50% of the cases are high-risk tumors with a high probability of relapse and a very low overall survival rate (< 40%). Although polychemotherapy elicits a good initial response in most NBs, tumors frequently relapse after the expansion of resistant tumor cell clones. Intratumor heterogeneity (ITH) has been described as a major cause for resistence and treatment failure in several tumor entities. In neuroblastoma, however, the extent of ITH is thus far unknown. To investigate ITH and to better unterstand tumor evolution in neuroblastoma, we performed a multi-region whole-exome sequencing (WES) on a total of 29 spatially separated tumor regions from 7 neuroblastoma patients, 2 with low risk and 5 with high-risk disease. In order to increase the sensitivity for low abundant genetic aberrations, we macrodissected areas with high tumor purity from tumor cryosections. Sequencing data were generated for tumor regions and matching normal control samples to a mean exome coverage of 100x. We identified a wide range of somatic single nucleotide variations (SNVs) ranging from 20 to 170 per tumor region. We classified each mutation as ubiquitous (present in all tumor regions of one tumor) or specific (only in 1 region) and found 30 to 90% specific mutations reflecting a high rate of spatial heterogeneity in NB. Importantly, spatial genetic heterogeneity was also apparent for recurrent mutations of cancer related genes in high-risk tumors, indicating that ITH in NB has relevant clinical implications.

Screening 1505 kinase inhibitors across lung cancer cell lines reveals CDK9 as a synthetic lethal target in NUT midline carcinoma

MILES

Presenting Author: Johannes Brägelmann

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A major cornerstone of modern precision cancer medicine is the application of targeted therapies to efficiently inhibit signaling pathways that genetically altered in cancer e.g. due to mutations. However, only a minority of oncogenic drivers is directly druggable. The scope of potential targets may be expanded by exploiting synthetic lethality, i.e. inhibition of an unaltered protein required for cell viability in a certain genetic background. To identify novel synthetic lethal dependencies, we performed a chemo-genomic analysis of 1505 small molecular compounds tested against 78 genomically annotated non-small cell lung cancer cell lines. Systematic analysis of genotype-specific dependencies revealed that CDK9 inhibition (CDK9i) exhibits selective and robust activity against NUT-midline carcinoma (NMC) cells, an entity characterized by recurrent BRD4-NUT gene fusions and sensitivity to bromodomain inhibition (BRDi) supposedly due to interference with Myc expression. Interestingly, BRDi predominantly led to p21-dependent cell cycle arrest and cell differentiation in NMC, while both CDK9i and CDK9/Cyclin-T1 knock-down led to induction of apoptosis. Accordingly, only CDK9i strongly reduced anti-apoptotic MCL1 and induced markers of DNA damage, while both BRDi and CDK9i decreased Myc levels over time in NMC cells, but not in control cell lines. Additional RNA-Seq and ChIP-qPCR assays revealed a CDK9i-induced perturbation of transcriptional elongation in NMC with a bi-phasic impact on MYC target genes. Overall, this indicates distinct mechanisms of action for CDK9i compared to BRDi in NMC and lineage-specific effects of CDK9i on Myc signaling. In conclusion, our systems-level approach allowed us to uncover a novel synthetic-lethal dependency in NMC and provides a mechanistic basis that may aid future therapeutic strategies for NMC patients.

Investigation of Drug Tolerant Persister Cells in EGFR-mutated lung adenocarcinoma

MILES

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Therapy outcome of EGFR-mutated lung adenocarcinoma towards targeted therapy is limited by the development of acquired resistance in nearly all cases. By temporary acquisition of a drug tolerant persistent phenotype subpopulations of EGFR-dependent cancer cells can survive otherwise lethal EGFR-inhibition, and evolve towards a fully resistant phenotype. Such drug toleratent persister cells (DTPs) may contribute to the clinically observered development of acquired resistance upon treatment with EGFR-inhibitors and approaches preventing or directly targeteting DTPs will likely improve therapeutic outcome. However, the cellular mechanisms which enable cells to evade cell death and adapt under prolonged drug exposure, making them DTPs, remains incompletely understood. To investigate adaptational processes leading to DTP formation, we performed transcriptional analysis of EGFR-mutated cell lines at multiple time points upon treatment with an EGFR-inhibitor. We find that in response to acute drug exposure, cell lines show immediate changes in feedback regulation of MAPK signaling. Furthermore, cells that survive prolonged drug exposure display changes in cell cycle progression which are consistent with the non-proliferative phenotype observed. Additionally, these cells upregulate interferon signaling. We are currently investigating the mechanisms underlying these changes and predict that we will hereby identify vulnerabilities specific for drug tolerant persister cells, from which combinatorial approaches that delay or prevent development of acquired resistance could be developed.

Effects of trastuzumab and afatinib on kinase activity in gastric cancer cell lines

SYS-Stomach

Presenting Author: Gwen Zwingenberger

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The molecular mechanism of action of the HER2-targeted antibody trastuzumab is only partially understood, and the direct effects of trastuzumab on the gastric cancer signaling network are unknown. In this study, we compared the molecular effect of trastuzumab and the HER kinase inhibitor afatinib on the receptor tyrosine kinase (RTK) network and the downstream-acting intracellular kinases in gastric cancer cell lines. The molecular effects of trastuzumab and afatinib on the phosphorylation of 49 RTKs and 43 intracellular kinase phosphorylation sites were investigated in three gastric cancer cell lines (NCI-N87, MKN1 and MKN7) using proteome profiling. To evaluate these effects, data were analyzed using mixed models and clustering. Our comprehensive quantitative analysis of kinase activity in the gastric cancer cell lines indicates that trastuzumab and afatinib selectively influenced the HER family RTKs. The effects of trastuzumab differed between cell lines, depending on the presence of activated HER2. The effects of trastuzumab monotherapy were not transduced to the intracellular kinase network since the investigated intracellular kinases were not regulated by trastuzumab. Afatinib alone or in combination with trastuzumab had effects on HER kinases in all cell lines, that is, the effects of monotherapy and combination therapy were transduced to the intracellular kinase network. The dependence of the effect of trastuzumab on the presence of activated HER2 might explain the clinical non-response of some patients who are routinely tested for HER2 expression and gene amplification in the clinic but not for HER2 activation. The consistent effects of afatinib on HER RTKs and downstream kinase activation suggest that afatinib might be an effective candidate in the future treatment of gastric cancer patients irrespective of the presence of activated HER2.

Central validation of HER2 status to determine heterogeneity of marker expression in HER2 positive gastric cancer (GC)

SYS-Stomach

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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 directed against HER2 have shown mixed success in the treatment of advanced GC. While trastuzumab, a monoclonal antibody addressing HER2 has been approved for 1st-line treatment of stage IV HER2+ GC, trastuzumab-emtansine failed to improve outcomes in 2nd-line and lapatinib, a small molecular RTK inhibitor of HER2 and EGFR was not effective in 1st- and 2nd-line. Until now, primary and secondary resistance against HER2-directed treatment of GC is not well understood. The VARIANZ study aims to assess mechanisms influencing efficacy of trastuzumab in HER2+ GC.

Methods: In this multicenter study, patients who receive medical treatment for advanced GC are recruited in 34 sites. The HER2 status is verified centrally by two dedicated GI pathologists using immunohistochemistry (IHC, DCS, HI608C0I) and chromogenic-in-situ hybridization (CISH, Zytomed Systems, C-3022-40).

Results: From May 2014 to July 2017, we have enrolled 463 patients in this ongoing project. At present, 414 samples were fully characterized for the HER2 status. According to criteria from the Trastuzumab for Gastric Cancer (ToGA) study, 73 of 414 samples were characterized HER2+ by central testing. In 54 samples that were diagnosed as HER2+ by local pathologists the HER2 status could not be verified centrally. 10 HER2- probes in local testing were characterized as HER2+ by central testing. The overall deviation rate between local and central testing is 23%.

Conclusions: HER2-expression in GC is heterogeneous and still not easy to assess. Variability between local and central HER2 assessment is significant. Robust biomarkers predicting response or resistance to HER2 and other target therapies are needed.

Hodgkin lymphoma cells trigger in vitro differentiation of human monocytes into macrophages of the M2-subtype

MMML-Demonstrators

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Interactions between tumor cells and microenvironment crucially regulate disease progression, including tumor cell survival, metastasis and therapy resistance. A paradigmatic microenvironment-controlled cancer entity is classical Hodgkin lymphoma (HL). The malignant Hodgkin-Reed-Sternberg (HRS) cells account for less than 1 % of the disease-related cells. The role of macrophages in lymphoma development and dissemination is currently under intensive debate. Notably, several studies reported on more rapid disease progression and even treatment failure in patients with high numbers of macrophages in the lesions. Tumor-associated macrophages have often been assigned as tumor-supportive microenvironmental cells, able to sustain proliferation and angiogenesis and to suppress anti-tumor immune responses. Therefore, the aim of our study is to characterize mutual interactions between HRS cells and monocyte-derived macrophages. Primary human monocytes were differentiated in vitro in the presence of lymphoma-conditioned supernatant or colony-stimulating factor 1 (CSF1/M-CSF). Gene expression, cell surface protein expression and metabolites were measured using qRT-PCR/RNA-Seq and flow cytometry. The HL-secretome strongly support monocyte differentiation into macrophages, specifically the M2-related subtype. These macrophages are characterized by strong expression of CD40, CD68, CD163, CD206, and significant expression of adhesion molecules. Functional analyses revealed high endocytic activity of the HL-conditioned macrophages. In addition, we used chick chorioallantoic membrane assays to study the role of the M2-related macrophages for lymphoma behavior in ovo. Our observations support a model in which HRS cells are able to induce monocyte differentiation into M2-related macrophages, which then modulate the lymphoma microenvironment.

Molecular signatures that can be transferred across different omics platforms

MMML-Demonstrators

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Motivation: Molecular signatures for treatment recommendations are well researched. Still it is challenging to apply them to data generated by different protocols or technical platforms.

Results: We analyzed paired data for the same tumors (Burkitt lymphoma, diffuse large B-cell lymphoma) and features that had been generated by different experimental protocols and analytical platforms including the nanoString nCounter and Affymetrix Gene Chip transcriptomics as well as the SWATH and SRM proteomics platforms. A statistical model that assumes independent sample and feature effects accounted for 69% to 94% of technical variability. We analyzed how variability is propagated through linear signatures possibly affecting predictions and treatment recommendations. Linear signatures with feature weights adding to zero were substantially more robust than unbalanced signatures. They yielded consistent predictions across data from different platforms, both for transcriptomics and proteomics data. Similarly stable were their predictions across data from fresh frozen and matching formalin-fixed paraffin-embedded human tumor tissue.

Availability: The article “Molecular signatures that can be transferred across different omics platforms” is available under [1] and the R-package “zeroSum" can be downloaded at https://github.com/rehbergT/zeroSum.

[1] M. Altenbuchinger, P. Schwarzfischer, T. Rehberg, J. Reinders, Ch. W. Kohler, W. Gronwald, J. Richter, M. Szczepanowski, N. Masqué-Soler, W. Klapper, P. J. Oefner, R. Spang; Molecular signatures that can be transferred across different omics platforms, Bioinformatics, Volume 33, Issue 14, 15 July 2017, Pages i333–i340, https://doi.org/10.1093/bioinformatics/btx241

Harnessing the predictive potential of tumor heterogeneity via the integration of MALDI imaging data and dynamic modeling

SYSIMIT

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Tumor heterogeneity has been recognized a primary factor of tumor resistance against therapy. However, until now the heterogeneity information was not contributing in the prediction of tumor growth. This relies in two reasons: (i) there is not a unifying and reliable heterogeneity measure, and (ii) the existing measures are not used into predictive models of tumor growth dynamics. Here, we use the MALDI imaging data of tumor samples to extract information about the sample's heterogeneity. In turn, we focus on developing a novel heterogeneity index to accurately quantify the variety of tumor clones and other cell types in a tumor biopsy. Moreover, applying spatial statistical measures inspired by statistical physics, we elucidate additional information about the spatial structure of the sampled tumor. Finally, we showcase how to integrate the above information in an agent-based model of tumor development and growth. This unique combination of MALDI imaging data and mathematical modeling will be further applied in understanding the growth dynamics and therapy resistance in gastric tumors.

Synergistic co-treatment and targeting of tumor-associated antigens increase the apoptotic activity of TRAIL fusion proteins on melanoma cells

Melanoma sensitivity

Presenting Author: Martin Siegemund

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We have recently developed single-chain formats of TNF-related apoptosis inducing ligand (scTRAIL), being characterized by increased thermal stability and high tumor cell-specific induction of apoptosis. These molecules may serve as important components of tumor-associated antigen-targeted as well as non-targeted fusion proteins for treatment of melanoma. A hexavalent arrangement of TRAIL was realized with epidermal growth factor receptor (EGFR)-targeted Db(diabody)-scTRAIL as well as melanoma-associated chondroitin sulfate proteoglycan (MCSP)-targeted and HER3-targeted scFv-Fc-scTRAIL, respectively. All protein formats ensure effective activation of death receptors DR4 and DR5 and display a good safety profile in vivo. In addition, an anti-EGFR hu225 IgG served as a platform for generation of hexavalent or dodecavalent scTRAIL fusion proteins (IgG-scTRAIL). Already the non-targeted Fc-scTRAIL proved to be an effective inducer of cell death in both, BRAF and NRAS mutated melanoma cell lines. However, antigen-targeted formats like scFv(MCSP)-Fc-scTRAIL exceeded the activity of Fc-scTRAIL with up to ~20-fold lower EC50 values (e.g., 0.5 pM on WM3060 cells). In terms of sensitization to TRAIL induced cell death, bortezomib proved to be more effective than the BRAF inhibitor dabrafenib or the MEK inhibitor trametinib in a panel of different melanoma cell lines. Strikingly, also under conditions of low EGFR or MCSP antigen expression on the tumor cell, hexavalent antigen-targeted scTRAIL fusion proteins possessed approximately one order of magnitude higher bioactivity compared to non-targeted Fc-scTRAIL. Our results show that engineering of fusion protein formats with hexa- or dodecavalent TRAIL configuration in combination with apoptosis sensitizers and/or antigen targeting represents a promising approach for effective therapy of melanoma.

Sequential Organ Failure Assessment (SOFA) Score as Operationalization of Disease Severity of hospitalized Community acquired Pneumonia (CAP)

CAPSyS

Presenting Author: Peter Ahnert

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Purpose: CAP (Community acquired pneumonia) is a frequent infectious disease with high mortality and a high burden on health care systems. Development of predictive biomarkers, new therapeutic concepts and epidemiologic research requires a valid, reproducible, and quantitative outcome measure describing CAP severity from uncomplicated to critical disease state. Scores evaluating severity of patients with infectious diseases were proposed in the literature. We aim to determine which serves this purpose best.

Patients and methods: Using time series data of the first 1,532 patients enrolled in the multi-center PROGRESS study, we compared measures of CAP severity with respect to performance in correctly identifying patients with an objectively severe state of disease (death or need for intensive care with at least one of the following: substantial respiratory support, treatment with catecholamines, or dialysis). CRB-65, CURB-65, PSI, SIRS-Score, SOFA, qSOFA, Halm criteria, SCAP, SMART-COP, CRP, and PCT were compared by receiver operating characteristics using R. Patients of the PROGRESS cohort were younger than the overall population of patients hospitalized for CAP in Germany (median of 59 vs. 73 years) and showed lower in-hospital mortality (2.3% vs. 13.9%).

Results: SOFA significantly outperformed all considered alternatives in detecting patients with a severe state of disease at the day of enrolment (AUC = 0.948), caused by higher discriminative power at higher score values. SCAP was the runner up (AUC = 0.868). SOFA performed similarly well on subsequent study days (all AUC > 0.9). In univariate and multivariate analysis, age, sex, and pack-years significantly contributed to higher SOFA values whereas antibiosis before hospitalization predicted lower SOFA.

Conclusion: SOFA is an excellent candidate for operationalization of CAP severity, facilitating biomarker and therapeutic studies. Validation in a representative CAP population is required.

Macrophages render lung epithelial cells hypo-responsive to Legionella pneumophila – a systems biology study

CAPSyS

Presenting Author: Bernd Schmeck

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Immune response in the lung has to protect the huge alveolar surface against pathogens while securing the delicate lung structure. Macrophages and alveolar epithelial cells constitute the first line of defense and together orchestrate the initial steps of host defense. In this study, we analysed the influence of macrophages on type II alveolar epithelial cells during Legionella pneumophila-infection by a systems biology approach combining experimental work and mathematical modelling. We found that L. pneumophila-infected macrophages provoke a pro-inflammatory activation of neighboring lung epithelial cells, but in addition render them hypo-responsive to direct infection with the same pathogen. We generated a kinetic mathematical model of macrophage activation and identified a paracrine mechanism of macrophage-secreted IL-1β inducing a prolonged IRAK-1 degradation in lung epithelial cells. This intercellular crosstalk may help to avoid an overwhelming inflammatory response by preventing excessive local secretion of pro-inflammatory cytokines and thereby negatively regulating the recruitment of immune cells to the site of infection. This suggests an important but ambivalent immunomodulatory role of macrophages in lung infection.

Inflammatory bowel disease progression is associated to epigenetic regulators and their target genes

SysINFLAME

Presenting Author: Robert Häsler

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Inflammatory bowel disease (IBD) with its major subforms Crohn's disease (CD) and ulcerative colitis (UC) is a chronic inflammation, which displays a heterogeneous clinical disease progression. While the symptoms of some patients can be stabilized over a long time, others exhibit severe complications such as fistulae, dysplasia or colorectal cancer. Although it is unclear which mechanisms contribute to these differences and what determines a more severe disease course, it has been shown that epigenetic regulation of disease-associated mechanisms is associated to IBD. Consequently, different epigenetic events could contribute to altered disease progression in IBD. To investigate the potential impact of functional epigenetic modifications, we monitored transcript levels and DNA-methylation in a genome wide manner in n=35 IBD patients at different disease progression states. To refine our picture, five different disease categories were selected (CD non-complicated, CD stenosis, CD neoplasia, UC non-complicated, UC colorectal cancer) while spanning a monitored disease duration of 2-13 years. Preliminary results were showing a strong link between disease progression associated mechanisms and corresponding epigenetic regulators. The resulting model was then exploited to determine the molecular disease age of individual patients on a continuous disease progression scale. Interestingly, patients with a more severe phenotype showed a more advanced molecular disease age, reflecting their faster disease progression. In conclusion, our findings indicate that specific functional epigenetic modifications represent a valuable proxy for disease progression in IBD. Furthermore, molecular patterns obtained at early disease stages contain vital information on the potential future disease progression of IBD in individual patients.

Investigation of comorbidity and therapy response using transcriptional signatures across chronic inflammatory diseases

SysINFLAME

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Chronic inflammatory diseases (CIDs) are characterized by a high rate of comorbidity and a frequent lack of therapy response. Understanding the molecular mechanisms underlying CID co-occurrences as well as predictions of drug response are of crucial importance to device more specifically tailored treatment strategies for patients affected by one or several CIDs. Using 3783 published transcriptome samples across five CIDs (chronic obstructive pulmonary disease, coronary artery disease, inflammatory bowel disease, periodontitis, and psoriasis), we identified a core inflammation signature comprising 732 genes enriched for 28 pathways and thus, dissected general causal from tissue-specific changes. Compared to disease-specific dysregulated genes, core inflammation genes were characterized by a higher average network connectivity as well as a higher proportion of genes associated with the immune system. Interestingly, disease distances based on expression data showed a high similarity to reported comorbidity rates between diseases. This demonstrates that the likelihood of comorbidities is reflected in the expression data even before occurrence of a second disease. Additionally, a drug response prediction (DRP) approach for CIDs was implemented and verified with several studies. Besides applications in personalized medicine, this approach can be used for guiding the development of novel drugs to avoid extensive lab experiments. Already performed in silico predictions of the transferability of 13 known drugs showed a very strong concordance with phase 1-3 clinical trials. Combining the cross-disease approach with DRP is important to identify the optimal therapy approach for comorbid patients and can give additional insights into gene characteristics of the most promising drug targets. In summary, this project is a key step towards understanding comorbidity and supporting therapy decisions as well as the development of novel drugs in CIDs.

Network coherences - a universal approach to quantify the match between 'omics' data and a biological network

SysINFLAME

Presenting Author: Piotr Nyczka

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Network-based analyses of 'omics' data are a cornerstone of systems medicine. Their goal is to quantify and statistically evaluate the clustering of biological signals (e.g., co-expression of genes) in a network (e.g., a metabolic network or a protein-interaction network). Network coherences are topological indices evaluating the connectivity of subnetworks spanned by the 'omics' signal of interest [1,2]. They have been used very successfully to identify scientifically relevant patient subgroups in disease cohorts [2-4]. Here, we aim at a deeper theoretical understanding of network coherence. Using various random walk models on graphs, we test, refine and calibrate this method. In this way, the dependence of a given network coherence upon the number of disease-associated genes, the topology of the underlying biological network or the fragmentation of the functional signal in the network can be studied numerically and compared to analytical predictions. Based upon our results, we also present a range of applications of (metabolic) network coherence to the analysis of transcriptome profiles in chronic inflammatory diseases. Extending the notion of metabolic network coherence from [2,3] to individual patients, we can identify inter-individual differences in disease coping at the metabolic level. This approach represents a first step towards using network signatures in personalized medicine. [1] Sonnenschein, Geertz, Muskhelishvili, Hütt (2011) BMC Systems Biology 5, 40. [2] Sonnenschein, Golib Dzib, Lesne, Eilebrecht, Boulkroun, Zennaro, Benecke, Hütt (2012) BMC Systems Biology 6, 41. [3] Knecht, Fretter, Rosenstiel, Krawczak, Hütt (2016). Scientific Reports, 6. [4] Häsler, Sheibani-Tezerji, Sinha, Barann, Rehman, Esser, Aden, Knecht, Nikolaus, Schäuble, Kaleta, Franke, Fretter, Müller, Hütt, Krawczak, Schreiber, Rosenstiel (2016). Gut, gutjnl-2016-311651.

Insights into the shared aetiology of atopic dermatitis, asthma and hay fever

SysINFLAME

Presenting Author: Hansjörg Baurecht

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Atopic dermatitis, asthma and hay fever are often observed within the same individuals, partly because of a shared genetic background. So far, 15 shared genetic risk factors have been identified by single-disease genome-wide association studies (GWAS), but most remain uncharacterized. We performed a GWAS (n=360,838) of a broad allergic disease phenotype that considers the presence of any one of these three. We carried out extensive follow-up and enrichment analysis to understand biological consequences. Plausible target genes were defined by identification of coding variants, expression quantitative trait locus and publicly available functional data. The target genes were carried forward to identify enriched pathways as well as disproportional overexpression in different tissues and cell types exploiting publicly available data. Using integrative omics data we searched for cis expression quantitative methylation potentially modulating target gene expression by environmental risk factors. We identified 136 independent risk variants (P<3x10-8) including 88 novel variants. Disease-specific effects were detected for only six variants, confirming that most represent shared risk factors. There were 244 likely target genes of risk variants, including 131 (54%) not previously implicated in allergic disease pathophysiology. We observed a significant enrichment of target gene expression SNP heritability amongst immune cell subsets (e.g. BAFF+ T cells, CD56+ NK cells), with weaker but detectable effects in lung and skin. For 81 target genes we found CpG methylation that influence transcription independently of genetic effects. Our results demonstrate that asthma, hay fever and eczema coexist to a large extent because they share many genetic risk variants that dysregulate the expression of mainly immune-related genes. Finally, our results suggest that environmental factors such as smoking might influence allergic disease risk through modulation of target gene methylation.

Investigation of the genetic architecture of metabolic coherence

SysINFLAME

Presenting Author: Kristina Schlicht, Carolin Knecht

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Metabolic Coherence (MC) is a network-driven dimension reduction approach facilitating the interpretation of the expression of genes associated with human metabolism. The genetic architecture of MC, i.e. the identity and function of genes associated with MC, is however still largely unclear.
We calculated MC values from the expression data of the 1000 Genomes Projecta (excluding the Yorubian population) using the Recon2-Networkb and performed a GWAS to search for QTLs. Several SNPs associated with MC were identified in the intronic region of the Cadherin 18 gene (CDH18) on chromosome 5. CDH18 is a transmembrane protein that is involved in human neural development during early embryogenesis and in cell-to-cell signalling.
Validation of the 1000 Genomes findings in a US-based cohort (GENOA study, Mayo clinic) is currently underway. Preliminary comparison of the gene expression data from GENOA and 1000 Genomes revealed differences regarding the individual-specific subnetworks of saliently expressed genes.
To further elucidate the role of the CDH18 region, we performed a trans-eQTL analysis using only expression data for Recon2-genes and genotypes of 280 SNPs near the top GWAS hit. We identified a number of genes expression of which appears to drive the GWAS signal.
Our findings provide new information about the genetic structure of MC and thereby contribute further to a more general understanding of human metabolism.

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Measurement of calprotectin in an IBD kindred cohort in Germany

SysINFLAME

Presenting Author: Marie Tempel

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Background: Inflammatory bowel disease (IBD) clusters in families. To identify clinical and molecular predictors of IBD, a longitudinal IBD family cohort was established, which includes affected and unaffected family members of IBD patients and collects biosamples and health-related information on a regular basis.

Methods: Every 2 years, health-related information and biosamples (blood, stool, hair) are being collected from the participants of the cohort. The self-administered questionnaire covers socio-demographic characteristics, lifestyle factors, medical history, including co-morbidities, therapy, dietary intake and physical activity. Calprotectin in stool has been measured using a commercial ELISA (Bühlmann fCALTM).

Results: The IBD family cohort currently includes 1059 individuals (393 singletons or families; 450 affected, 583 unaffected). 99 probands were underage. Family size ranged up to 9 individuals per family. The average duration of IBD in patients was 16.6 ±12.1 years. Data and biosamples from the first follow-up (2-years) have been collected from 636 individuals (ongoing). So far, 2 initially healthy participants developed a new-onset (incident) IBD since inclusion into the study (0.3%). As expected, average calprotectin values (mg/kg stool) were highest in IBD participants (median: 41.6, Q1: 19.6, Q3: 175.6, n=432) and much lower in unaffected first-degree relatives (median: 20.6, Q1: 10.5, Q3: 39.1, n=406, $p<0.0001$).

Conclusion: Repeated collections of biosamples and health-related information in healthy family members of IBD patients and the longitudinal tracking of such families offers new research opportunities regarding predictors and biomarkers of early stages of IBD. Calprotectin in stool of IBD patients was significantly higher as compared to their clinically healthy relatives. An ongoing follow-up of this cohort will reveal whether calprotectin might serve as a biomarker to identify future cases of IBD before the onset of clinical symptoms.

Systems diagnostic of the human gut microbiome on inflammatory diseases using metaproteome analysis of fecal samples

Presenting Author: Theresa Schlegel

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Crohn's disease (CD) and Ulcerative Colitis (UC) are chronic inflammatory bowel diseases (IBD), which are associated with alterations in gut barrier function, mucosal inflammation and in gut microbiome. The impact of the inhabited microbiome on the gut system is poorly understood. The gut microbiome comprises about 1013 microorganisms which have several metabolic functions. Furthermore, the microbiome interacts with the host influencing directly the immune system. For understanding of the interactions between the gut mucosa and the microbiome, proteins in fecal samples from patients with IBD (nCD=11; nUC=14), irritable bowel syndrome (IBS) (nIBS=13) and healthy individuals (ncontrol=17) were analyzed using metaproteomic. The aim of this study was to correlate microbial taxonomies or metabolic functions with an increased inflammatory level of the human gut and to identify marker proteins. The workflow comprised protein extraction with liquid phenol in a ball mill, tryptic digestion of the complete sample and peptide separation by liquid chromatography coupled to an Orbitrap MS/MS. For protein identification, taxonomic and functional result interpretation the MetaProteomeAnalyzer software and a tailored protein database consisting UniProtKB/SwissProt as well as several metagenomes from human fecal samples were used. Analysis of the fecal samples identified up to 3000 metaproteins from human as well as from bacteria, archaea and viruses. IBD affected the functional and taxonomic composition of the metaproteins in fecal samples. Among others, carbohydrate metabolism and protein biosynthesis of the bacteria were down regulated in all IBD samples, whereas the biological processes of inflammatory and adaptive immune system of the host were only up regulated in active UC samples. At taxonomic level, especially in the order of clostridiales the amount of microbial metaproteins in IBD samples seems to be decreased compared to the controls.

Detection of Human Biomarkers for Diagnosis and Treatment of Invasive Fungal Infections

Presenting Author: Jörg Linde

Jörg Linde(1), Michael Weber(1), Tamara Zoran(1,2), Jürgen Löffler(2)

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During the last decades the number of individuals with a weakened immune status has been growing in the western world, mainly due an ageing society. Elderly persons not only often have a weak immune system, they also are at higher risk for cancer and often undergo large surgeries. As a weak immune status raises the risk of infections, we need better biomarkers for diagnosis and to support treatment decisions for individual medicine. Since many pathogens occur only transiently in specific tissue or blood, studying host factors is a promising approach. For this purpose, the Junior Research Group PiDOMICs aims to identify human biomarkers. As an example, we work with data from patients who underwent stem-cell transplantation and identify biomarkers for infection with Aspergillus fumigatus - the major airborne fungal pathogen which causes mortality rates up to 80%. Therefore, we combine personal information of patients (e.g. age, sex) with their medical status (e.g. blood cell counts), as well as transcriptomics and proteomics data. Here, I will present first results. In a pioneering study, we constructed a classifier based on transcriptional biomarkers in whole blood of donors which robustly discriminants bacterial from fungal infections and thus may support early therapeutic decisions (anti-biotics vs mycotics) for septic patients (Dix 2015 Front Microb). Next, we found first hints of microRNAs which are specifically regulated in dendritic cells as response to fungal infections (Dix 2017 Front Microb). Moreover, we used expression data from patients after stem-cell transplantation in a Random Forest approach to identify genes whose expression discriminates patients with and without Aspergillus infection. Thereby we identified the calcium binding protein S100B as promising diagnostic biomarker (Dix 2016 Front Microb). Finally, we utilized time-resolved clinical data and to identify significant associations between clinical features and Aspergillus infection.

Reconstructing lipid peroxidation products (LPPs) metabolic networks for systems medicine view on obesity and type II diabetes.

SysMedOs

Presenting Author: Georgia Angelidou

Georgia Angelidou, Zhixu Ni, Maria Fedorova

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Many human diseases, including obesity, diabetes and atherosclerosis, are accompanied by chronic inflammation and closely connected to oxidative stress (OS). OS can oxidize virtually all biomolecules of which lipids represent one of the most prominent targets. Lipid peroxidation products (LPPs) are chemically diverse group of biomolecules with a variety of functional activities. Many LPPs were shown to play an important role in the onset and development of OS-related diseases and can serve as diagnostic and prognostic biomarkers. However, to include LPPs in a systems medicine view on obesity, the information on their structures, activities and functions as well as associations with various pathological conditions need to be collected and summarized. Two types of comprehensive meta-studies aiming to integrate existing information on lipid oxidation and it relevance to obesity and type II diabetes were conducted. The first study focused on the enzymatic and non-enzymatic LPPs production. Based on the information extracted from more than 170 peer-reviewed publications, networks of enzymatic and free-radical-driven oxidation were reconstructed for the most abundant polyunsaturated fatty acids. Reconstructed networks allowed to illustrate differences and similarities in PUFAs oxidation mechanisms and were further used to design predictive in silico oxidation algorithms. Reconstructed networks were used as a basis for the second meta-study focusing on the role of LPPs in obesity and diabetes II type in adipose tissue and plasma samples. The information about the role of LPPs in different disease related pathways will be used for the enrichment of the reconstructed networks creating more complex metabolic networks of phospholipids oxidation. Identified pathways will be implemented into Reactome pathway database and further used to for the integration of experimental data sets.

Prediction of glucose tolerance without an oral glucose tolerance test

Presenting Author: Robert Wagner

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Background: Impaired glucose tolerance (IGT) can be diagnosed by a standardized oral glucose tolerance test (OGTT). However, the OGTT is laborious and when not performed, glucose tolerance cannot be determined from fasting samples retrospectively. We tested if glucose tolerance status is reasonably predictable from a combination of demographic, anthropometric and laboratory data assessed at one timepoint, in a fasting state.

Methods: Given a set of 22 variables selected upon clinical feasibility such as sex, age, height, weight, waist circumference, blood pressure, fasting glucose, HbA1c, hemoglobin, mean corpuscular volume, serum potassium, fasting levels of insulin, C-peptide, triglyceride, non-esterified fatty acids (NEFA), proinsulin, prolactin, cholesterol, LDL, HDL, uric acid, liver transaminases and ferritin, we used supervised machine learning to estimate glucose tolerance status in 2337 participants of the TUEF study recruited before 2012. We tested the performance of 10 different machine learning classifiers on data from 929 participants in the test set that was recruited after 2012. Additionally, reproducibility of IGT was analyzed in 78 participants who had 2 repeated OGTTs within a year.

Results: The highest overall unbiased accuracy in the prediction of IGT was reached with a recursive partitioning and a stochastic gradient boosting method (kappa=0.42), but model performance measures did not differ greatly (mean kappa=0.39±0.03). The most important model variable was fasting glucose in all models. Using mean variable importance across all models, fasting glucose was followed by HbA1c, NEFA, triglycerides and C-peptide. The accuracy of predicting IGT from a previous OGTT was 0.77, kappa=0.46.

Conclusion: Machine learning methods yield moderate accuracy in predicting glucose tolerance from a wide set of clinical and laboratory variables. This seems to be mostly limited by the low reproducibility of IGT during a subsequent OGTT.

Genetic determinants of aberrant splicing events in coronary artery disease

e:AtheroSysmed

Presenting Author: Baiba Vilne

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Coronary artery disease (CAD) and its clinical manifestations such as myocardial infarction (MI), remain among the leading causes of mortality worldwide, demanding a better understanding of the disease etiology and more efficient therapeutic strategies. CAD is a highly complex disease, influenced by both lifestyle and genetic factors. During the last ten years, the latter has been thoroughly-explored in numerous genome-wide association studies (GWAS), involving active participation of our research group. This has led to a successful identification of > 300 chromosomal loci which all significantly affect CAD/MI risk. However, the interpreation of their down-stream functional consequences has been challenging, thus far, considering that that >90% of these variants are located outside the protein-coding regions. Here, we want to study systematically whether CAD susceptibility SNPs exert their effects by affecting the patterns of alternative splicing of RNA transcripts. To that end, we have already established a (growing) bio-repository of >200 phenotypically and molecularly well-characterized CAD patients, each subjected to parallel sampling of whole blood, subcutaneous fat and internal mammary artery for RNA sequencing and DNA variation profiling, which is currently ongoing. We will utilize this unique resource to perform the first tissue-specific transcriptome wide mapping of the so called splicing quantitative trait loci (sQTL), which we will further integrate with transcript co-expression patterns, allowing us to determine their system-level impact on CAD. Furthermore, we aim to explore rare aberrant expression and splicing events associated with CAD risk, as well as to reconstruct transcriptome-wide gene regulatory networks (GRN) to predict the impact of non-coding genetic variation in enhancer elements. By this, we aim to pinpoint splicing-affecting genetic variants and predict their possible down-stream functional implications and therapeutic value to CAD/MI.

Associations between mental health, type-2 diabetes mellitus incidence, and human serum metabolome revealed by mixed graphical models

e:AtheroSysmed

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Recent studies suggest influences of a person's mental health on the incidence of type-2 diabetes mellitus (T2DM)1. Since exact underlying mechanisms still remain to be elucidated, we investigated the relationship between metabolome, mental health, and T2DM to gain further insights into pathogenesis. Importantly, we hypothesize that the underlying metabolic network will provide substantial insights into the mechanisms underlying the disease association. To this end, we analyzed 353 serum metabolites, measured by mass-spectrometry, in 1,411 participants of the KORA (Cooperative Health Research in the Augsburg Region) follow-up F4 study. Associations between metabolites and 10 different mental states, e.g. depression, or post-traumatic stress disorder, were analyzed by linear regression analysis with additional adjustment for 18 different covariates. We detected significant associations between several metabolites and self-reported health, type-D personality, and depression. Additionally, we observed gender-specific patterns, pointing towards a stronger effect of adverse mental health states on male than on female metabolism. To further explore the relationship between discrete mental health states, T2DM incidence, and continuous metabolite measurements, we calculated a mixed graphical model (MGM), a recent extension of graphical models for both continuous and discrete variables. These models identify correlations between two variables adjusted for all other variables. This analysis approach revealed a strong correlation between glucose and T2DM as a direct link between metabolism and T2DM, as well as minor associations between several metabolites and various mental health states. References: 1Huth, C., et al., Job Strain as a Risk Factor for the Onset of Type 2 Diabetes Mellitus: Findings From the MONICA/KORA Augsburg Cohort Study, Psychosomatic Medicine. 76(7):562–568, 2014.

Cysteine intestine rich protein 1 (Crip-1) – A novel blood pressure related candidate gene

symAtrial

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Hypertension is one of the most important risk factors of heart diseases. The investigation of blood pressure (BP) related genes in epidemiological cohorts as well as in experimental and clinical data through bioinformatic and statistical analyzes can lead to comprehensive understanding of mechanisms involved in hypertension and is important for system-medical approaches. In a large-scale population study CRIP1 (Cysteine-rich intestinal protein 1) was identified as the most strongly hypertension-associated gene in blood cells. In a clinical trial CRIP1 gene expression was reduced in response to antihypertensive treatment. Moreover, a strong correlation of CRIP1 expression with a reduced renal function was found. So far, the role of CRIP1 in the pathophysiology of hypertension is unknown and a renal-specific function as well as specific role in immune system are possible. The aim of this project is to identify the role of CRIP1 in development, regulation and maintenance of BP. Hence, we investigated the CRIP1 gene expression in proven hypertension mice models. Briefly, wild type or monocyte-depleted mice were treated with angiotensin II(AngII) in presence or not of deoxycorticosterone acetate (DOCA). We detected a significantly high expression of CRIP1 in kidneys of DOCA and AngII treated mice. Surprisingly CRIP1 expression in PBMCs in AngII-treated mice was significantly decreased. Further experiments indicated a significantly reduced CRIP1 expression in aorta of hypertensive mice. Interestingly this effect was abolished in monocyte-depleted mice. We also found a high expression of CRIP1 in human carotids plaques indicating the involvement of CRIP1 in atherosclerosis. BP is a complex process that is regulated by kidney and can be also influenced by immune system. CRIP1 might play an important role in these processes and contribute to define the underlying systemic mechanisms in hypertensive state. Furthermore CRIP1 could be used as a potential biomarker for high BP.

In silico analysis of candidate drug targets in the alpha-synuclein regulatory network

Mito-PD

Presenting Author: Enrico Glaab

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Abnormal aggregation and oligomerization of the protein alpha-synuclein (aSyn) is considered as one of the major pathological events in Parkinson's disease (PD) and other synucleinopathies. Genomic duplication and triplication of the gene was shown to be sufficient for causing PD, and variations in the promotor or 3'UTR region increasing its expression are associated with higher PD risk. Since previous studies suggest that it is technically challenging to develop therapeutic interventions which specifically target aSyn aggregation, investigating the druggability of endogenous protein regulators of aSyn, which modulate its expression, degradation or aggregation, may provide a means to identify and rank alternative candidate targets with favorable properties for drug design. Here, a bioinformatics analysis of the aSyn regulatory network is presented, mining the literature and public molecular interaction databases to find experimentally verified and putative aSyn protein modulators, and characterizing and scoring their druggability in silico. Published crystal structures for candidate protein targets are studied to identify binding pockets, and their suitability for small-molecule drug design is evaluated. Using omics data from PD case/control studies, genetic and transcriptomics alterations in the target genes are assessed for potential disease associations. Finally, the molecular network neighborhood and tissue specificity of the candidate targets is investigated to estimate potential adverse effects of modulating their activity. Overall, the implemented software pipeline for identifying aSyn protein regulators and scoring their suitability as potential drug targets provides an efficient approach to prioritize new candidate targets for subsequent validation in cellular models of PD.

Data-independent acquisition analysis of the mitochondrial proteome to identify quantitative, disease-specific signatures

Mito-PD

Presenting Author: Christian Johannes Gloeckner

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Parkinson disease (PD) is the second most common neurodegenerative disease and is characterised by the progressive loss of dopaminergic neurones from the substantia nigra, which eventually leads to a decline in patient motor function. The role of dysfunctional mitochondria in PD pathogenesis is becoming increasingly clear, with rare inherited forms of the disease highlighting signalling pathways that affect mitochondrial structure, membrane potential and clearance. Consequently, and in-depth, mass spectrometry (MS)-based analysis of the mitoproteome would likely reveal signalling networks involved in this impairment and could identify signalling pathways responsible for the pathogenesis of some forms of PD. By coupling an antibody-based mitochondrial isolation method with a data-independent acquisition (DIA) workflow, we achieved an in-depth proteomic interrogation of the mitoproteome while offering high-quality and consistent label-free quantification across many biological samples. The workflow employs a quartet of peptide database search engines, a series of the software packages offered by the Trans-Proteomic Pipeline, python scripts from the msproteomicstools package and Spectronaut (Biognosys). The hyper reaction monitoring (HRM) acquisition method was employed on the Q Exactive platform (Thermo) for all DIA experiments. The presented DIA workflow consistently detected a large fraction of these identified mitochondrial proteins reported in the MitoCarta 2.0 database (over 70%), including many components of the electron transport chain and proteins localised to endoplasmic reticulum-mitochondria contact sites. Following treatment with or without the uncoupler shows the developed workflow has a robust foundation and will have utility in unmasking the aberrant signalling that underlie mitochondrial dysfunction in neurodegenerative diseases, as well as other illnesses where mitochondria impairment is involved in disease pathogenesis.

Behavioral alterations in the Pink1-Q126P mouse model

Mito-PD

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Parkinson`s disease (PD) is the second most common neurodegenerative disease. The disease is characterized by its classical motor symptoms tremor, rigidity, bradykinesia and postural instability resulting from loss of dopaminergic neurons in the substantia nigra. Only about 10% of PD cases can be attributed to pathological mutations in the PARK loci, the remaining cases are sporadic. Several mutations in the gene encoding the PTEN induced kinase 1 (Pink1) cause autosomal recessive early-onset PD. PINK1 encodes a ubiquitously expressed 581-amino acid protein containing an N-terminal mitochondrial leader peptide (MTS), a transmembrane domain, and a highly conserved serine-threonine kinase domain. A majority of PINK1 mutations are found in the kinase domain, suggesting that the loss of its activity plays a crucial part in the pathogenesis of PINK1-linked PD. However, there are also mutations in the MTS and the transmembrane domain, the pathological consequences of which are not yet elucidated. In order to approach this question we have generated a new mouse model harboring the Pink1-Q126P mutation in the transmembrane domain by using the CRISPR/CAS technology. First behavioral analysis of the new mouse model show that they exhibit - as the knock-out - a deficit in a social discrimination task which is highly likely not due to an impairment in working memory, which was tested in the Y-maze. Interestingly however, and in contrast to the Pink1 deficient mice, olfactory dysfunction and alterations in gait were not observed. Rather there are indications for an altered anxiety related phenotype. Thus, the behavioral analysis of the new mouse line indicates that the Q126P mutation might induce different alterations than a complete loss-of-function mutation or a kinase dead mutation, respectively. The analysis of the underlying mechanisms inducing such differences is ongoing both in the mouse model and a human patient derived cellular model.

Glutamate-to-creatine ratio in the anterior cingulate cortex in alcohol withdrawal

SysMedAlcoholism

Presenting Author: Jens Treutlein

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The glutamate theory of alcoholism posits that increased glutamate-mediated neuronal excitability during withdrawal and abstinence contributes to craving and relapse processes in animals. Our human spectroscopic study aimed to test: (i) if the level of glutamate scaled to creatine (glutamate-to-creatine ratio; Glu/Cr) is increased in alcohol dependent cases during withdrawal compared to controls in the anterior cingulate cortex (ACC), a brain region important for the reward circuitry; and (ii) explore the contribution of genetic variation on this phenotype. Our study comprised 62 cases, the largest sample to date for the Glu/Cr phenotype in alcohol withdrawal, and 57 controls. We found an increase of the Glu/Cr ratio in patients compared to controls (P=0.026), and a negative association with age (P=0.001). Preliminary genetic analyses involved glutamatergic candidate genes and genetic risk scores from a GWAS of withdrawal symptoms. However, in both approaches, no significant association was found after correction for multiple testing. The best gene from the gene-based analysis of glutamatergic candidates in the 62 cases was GATA4 (gene-based P=0.0029). GATA4 influences the neuroendocrine regulation of stress, via atrial natriuretic peptide (ANP). A variant in its gene was initially identified in our GWAS on alcohol dependence, with support from a convergent approach that included differential expression in a rat model of chronic alcohol consumption. GATA4 was later replicated in an independent GWAS from the COGA study. A subsequent analysis in the PREDICT pharmacogenetics study showed the GATA4 variant to be associated with relapse. In conclusion, we could convincingly show in the largest sample to date, that withdrawal state is accompanied by an increase of Glu/Cr in the ACC, although no genetic association was found which survived multiple testing. This however does not exclude such an association, because our sample was comparatively small.

Oxytocin reduces alcohol cue-reactivity in alcohol dependent rats and humans

SysMedAlcoholism

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Approved pharmacological treatments for alcohol use disorder are limited in their effectiveness, and new drugs that can easily be translated into the clinic are warranted. One of those candidates is oxytocin because of its interaction with several alcohol-induced effects. Alcohol dependent rats as well as postmortem brains of human alcoholics and controls were analyzed for the expression of the oxytocin system by qRT-PCR, in situ hybridization, receptor autoradiography ([125I]-OVTA binding) and immunohistochemistry. Alcohol self-administration and cue-induced reinstatement behavior was measured after intracerebroventricular injection of 10 nM oxytocin in dependent rats. Here we show a pronounced up-regulation of oxytocin receptors in brain tissues of alcohol dependent rats and deceased alcoholics, primarily in frontal and striatal areas. This up-regulation stems most likely from reduced oxytocin expression in hypothalamic nuclei. Pharmacological validation showed that oxytocin reduced cue-induced reinstatement response in dependent rats - an effect that was not observed in non-dependent rats. Finally, a clinical pilot study using functional magnetic resonance imaging in heavy social male drinkers showed that intranasal oxytocin (24 IU) decreased neural cue-reactivity in brain networks similar to those detected in dependent rats and humans with increased oxytocin receptor expression. These studies suggest that oxytocin might be used as an anti-craving medication and thus may positively affect treatment outcomes in alcoholics.

Targeting GABAB receptor to treat drug addiction: benefits and pitfalls

SysMedAlcoholism

Presenting Author: Valentina Vengeliene

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During the recent years, GABAB receptor has received a remarkable attention as a potential target for treatment of substance use disorders. However, clinical studies report many adverse effects in patients using GABAB receptor agonist baclofen. No such poor tolerability profile was demonstrated in the preclinical studies. To get a better insight into this problem we employed two rat addiction models, which were developed in accordance with the Diagnostic and Statistical Manual of Mental Disorders, and are based on long-term drug consumption. Both models have been repeatedly used to study the neurobiological mechanisms underlying the transition from controlled to compulsive drug use and for testing of novel abstinence-promoting compounds. We examined whether baclofen and novel GABAB positive allosteric modulator CMPPE would effectively reduce alcohol and cocaine relapse-like behaviour, without inducing significant sedation. Our data showed that activation of the GABAB receptor by either baclofen or CMPPE did not abolish alcohol relapse, indicating that activation of this receptor is not sufficient to reduce relapse behaviour in alcohol addicted animals. The effective baclofen dose (3 mg/kg) was sedative and caused significant loss of body weight. This sedation was not observed in CMPPE treated rats. Cue-induced reinstatement of both alcohol- and cocaine-seeking behaviour was abolished by administration of both baclofen and CMPPE, suggesting a more general role of GABAergic system in drug-seeking responses. We conclude that therapeutic safety of CMPPE is within acceptable limits, whereas baclofen may cause not only sedation but also considerable impairment of food intake or metabolism. Targeting GABAB receptors may be more effective in reducing certain aspects of addictive-like behaviour, such as cue-reactivity.

Patterns of prefrontal cell firing during extinction learning and recall of alcohol-related memories in rats

SysMedAlcoholism

Presenting Author: Georg Köhr

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Understanding the neural basis of extinction and recall of alcohol-related memories will provide a cellular framework for pathomechanisms of alcoholism. Furthermore, to manipulate addictive alcohol behaviors specifically, characteristics of coherently active neurons representing alcohol- and extinction-associated memories are important to know. To examine them, we chose the medial prefrontal cortex (mPFC) which is involved in alcohol-seeking behavior based on ablation of activated neurons during recall or extinction. Naive rats were trained during operant alcohol self-administration to associate cues (light and 5 sec later lever presentation) with alcohol (10%) delivery in 60 trials per session. We recorded multiple single unit activity in rats implanted with tetrode wires within the mPFC when alcohol-related behavior was stable (conditioned or extinguished) and when alcohol-related behavior changed within a session (start of extinction and start of reacquisition). During the latter sessions the same neurons were investigated trial-by-trial. In 10 rats we detected about 140 active mPFC neurons. About 20% of them responded, either excitatory or inhibitory, to light and/or lever presentation within 500 and 300 ms, respectively. The excitatory responses were on average stronger than the inhibitory responses and remained constant during the behavioral sessions. Starting about 4 sec before lever presentation, we detected a ramping activity, either excitatory or inhibitory, reflecting reward (alcohol) expectancy. The number of active neurons doubled to about 40% in sessions with alcohol presentations. Upon analyzing neural activity based on resultant behavior (lever press or withhold), we found that cue-evoked activity switched from signaling press during alcohol-seeking to withhold in extinction. To further correlate behavior with neural activity on the single neuron level, we applied a sigmoidal learning model (see poster P 99 by Toutounji et al.).

Characterizing response and non-response to therapeutic sleep deprivation: clinical and genetic factors

IntegraMent, SysMedAlcoholism

Presenting Author: Jerome Clifford Foo

Nina Trautmann (1),(2) , Josef Frank (1), Stephanie H. Witt (1), Fabian Streit (1), Jens Treutlein (1), Steffen Conrad von Heydendorff (2), Maria Gilles (2), Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Andreas J. Forstner (3), Ulrich Ebner-Priemer (4), Markus M. Nöthen (3), Michael Deuschle (2), Marcella Rietschel (1)

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Research has shown that therapeutic sleep deprivation (SD) has rapid antidepressant effects in 50–70% of depressed patients. Investigation of factors preceding and accompanying these effects may facilitate the identification of the underlying biological mechanisms of both antidepressant response and depression. This exploratory study aimed to examine clinical and genetic factors predicting response to SD and determine the impact of SD on illness course. Mood and tiredness during SD were also assessed via visual analogue scales (VAS), characterizing the course of SD treatment. Depressed inpatients (n = 78) and healthy controls (n = 15) underwent ~36hrs of SD (August 2013-April 2015). Response to SD was defined as a score of ≤2 on the Clinical Global Impression Scale for Global Improvement. Depressive symptom trajectories were evaluated for up to a month using self and expert ratings. Impact of genetic burden was calculated using polygenic risk scores (PRS) for major depressive disorder. 72% of patients responded to SD. Response was associated with lower age ($p = 0.007$) and later age at life-time disease onset ($p = 0.003$). Higher PRS were observed in non-responders than healthy controls. Responders and non-responders did not differ in baseline self/expert depressive symptom ratings. However, they differed in mood, but not tiredness. Up to a month post-SD, depressive symptoms decreased in both patients groups, but more in responders, in whom effects were sustained. The present findings suggest that re-examining SD with a greater focus on biological mechanisms and using it as a model to understand transitions between disease states will lead to better understanding of mechanisms of depression.

Support for Contribution of Genetic Risk for Major Depressive Disorder to Alcohol Dependence

IntegraMent, SysMedAlcoholism

Presenting Author: Josef Frank

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Recently, Andersen et al. (2017; DOI:10.1001/jamapsychiatry.2017.2269) reported that higher polygenic risk scores for MDD were associated with increased risk for AD in four independent AD GWAS data sets explaining up to 2.6% of the variance in AD (Nagelkerke's R2). The authors suggested that larger MDD GWAS would improve the predictive ability of the derived PRS. This prompted us to examine the correlation between MDD and AD using data from the most recent and substantially larger PGC-MDD2 meta-analysis. In a sample of homogeneous German ancestry comprising 1333 male patients with severe AD and 1307 controls we calculated MDD-PRS. Regression analyses were performed on AD case-control. We observed significantly higher PRS in AD-cases than controls (p=3.4e-17, R2=3.3%). Moreover, increased MDD-PRS were similarly observed in a subsample of 332 AD patients collected explicitly excluding comorbid MDD (p=2.3e-6, R2=2.1%). This subsample did not differ significantly from the rest of the AD cohort (all p>0.2). In line with studies reporting an association of AD with Schizophrenia (SCZ), we further observe that PRS based on meta-analysis results from PGC-SCZ2 are significantly increased in AD cases (p=6.6e-8, R2=1.3%). However, the larger proportion of variance explained by MDD-PRS underlines the magnitude of overlap between AD and MDD. Our independent analysis confirms the contribution of genetic risk for MDD to AD; and we fully agree with Andersen et al. (2017) that increasingly large GWAS sample sizes will improve the ability of genetic approaches to target factors underlying AD and comorbid disorders.

Genetic Contribution to Alcohol Dependence: Investigation of a Heterogeneous German Sample of Individuals with Alcohol Dependence, Chronic Alcoholic Pancreatitis, and Alcohol-Related Cirrhosis

IntegraMent, SysMedAlcoholism

Presenting Author: Josef Frank

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The present study investigated the genetic contribution to alcohol dependence (AD) using genome-wide association data from three German samples. These comprised patients with: (i) AD; (ii) chronic alcoholic pancreatitis (ACP); and (iii) alcohol-related liver cirrhosis (ALC). Single marker, gene-based, and pathway analyses were conducted. A significant association was detected for the ADH1B locus in a gene-based approach (p_uncorrected = 0.000001; p_corrected = 0.02). This was driven by the AD subsample. No association with ADH1B was found in the combined ACP + ALC sample. On first inspection, this seems surprising, since ADH1B is a robustly replicated risk gene for AD and may therefore be expected to be associated also with subgroups of AD patients. The negative finding in the ACP + ALC sample, however, may reflect genetic stratification as well as random fluctuation of allele frequencies in the cases and controls, demonstrating the importance of large samples in which the phenotype is well assessed.

Early life stress in Schizophrenia: The role of microRNAs

IntegraMent

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Schizophrenia (SCZ) is a debilitating psychiatric illness affecting approximately 21 million people worldwide; it is more common among males (12 million), than females (9 million) (WHO, 2012). Apart from the genetic predisposition, environmental risk factors also play a role for developing SCZ. Early life stress (ELS) is one of these risk factors that also induce SZC-like phenotypes in mice. The present study sought to unravel differences in the peripheral small RNAome between SCZ patients that did or did not experience ELS. To achieve this 102 small RNAome datasets were sequenced from DSM-IV SCZ patient blood. This study includes 48 patients which experienced ELS and 54 which did not. We identified 14 miRNAs expressed differentially between both groups of which some have been linked to SCZ previously, DIANA miRPath indicated that miRNA-regulated pathways potentially down-regulated in SCZ are linked with long term depression, spliceosome while those up-regulated in SCZ are implicated in various signaling pathways e.g. hippo and MAPK signaling. To our knowledge, this is the first study to investigate the effects of ELS on small RNAs in SCZ patients.

Exome sequencing of multiply affected bipolar disorder families and follow-up resequencing implicate rare variants in neuronal genes contributing to disease etiology

IntegraMent

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Bipolar disorder (BD) is a severe and highly heritable psychiatric disorder affecting about 1% of the world's population. The disease is characterized by recurrent episodes of mania and depression. As the cumulative impact of common alleles may only explain ~38% of the phenotypic variance for BD, rare variants of high penetrance have been suggested to contribute to BD susceptibility. In this study, we performed whole-exome sequencing in 226 individuals of 68 large multiplex BD families of European origin. We filtered for rare (minor allele frequency < 0.1%), nonsynonymous, potentially functional and segregating variants. We identified 1214 variants implicating 1122 different genes. Gene enrichment analysis of 294 genes that were among the 20% most "intolerant" genes showed a significant enrichment for 18 pathways ($p<0.001$) including neuron projection and cell-adhesion. For follow-up analyses, we prioritized genes that were either found in at least two unrelated families in the present study or previously reported in next-generation sequencing or GWAS studies of BD. In addition, we enclosed genes that were predominantly driving the significant pathways in the above-mentioned gene enrichment analysis. The 42 most promising genes are currently being followed up by resequencing in larger cohorts of 2500 independent BD cases and 2500 controls of European ancestry using the single molecule molecular inversion probes (smMIPs) technology. The candidate genes include SYNE1, which is a genome-wide significant risk gene for BD. Our preliminary results strongly suggest that rare and highly-penetrant variants in neuronal and cell adhesion genes contribute to BD etiology. The results of resequencing of a large case/control sample will provide further evidence for an involvement of particular pathways in the pathophysiology of BD and related psychiatric disorders.

Exome sequencing in multiply affected families identifies new candidate genes for schizophrenia

IntegraMent

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Schizophrenia (SCZ) is a multifactorial psychiatric disorder with a lifetime risk of ~ 1% and a heritability of ~65%. Analysing multiply affected families using whole exome sequencing (WES) is a very promising approach to identify new SCZ risk factors. In these families, individuals are affected with SCZ over several generations. It is likely, that in multiply affected families genetic variations with particularly strong effect co-segregate with the disorder and contribute to the development of the psychiatric symptoms. We exome sequenced four genetically distant individuals from three multiply affected families, each. We performed both an analysis for structural variants and for rare (minor allele frequency ≤0.1%), single nucleotide variants that were shared between all affected individuals within the respective family. In addition, gene expression analyses and protein-protein-interaction analyses were conducted. In total, 35 single nucleotide variants and small indels that were predicted to be deleterious (Combined Annotation Dependent Depletion score ≥15; http://cadd.gs.washington.edu/) were identified. The protein-protein-interaction analyses showed that the set of candidate genes from our study has an overrepresented proportion of associations with SCZ-associated genes from the literature compared to a large reference gene set. Three genes were significantly differential expressed in SCZ patients compared to controls. To further evaluate the relevance of the new candidate genes in the pathogenesis of the disorder, we will sequence these in a large cohort of 5,000 individuals. Our work provides new insight into the genetic architecture of SCZ.

Hair Cortisol - Molecular and Formal Genetic Investigation of Genetic Overlap with Psychological Variables

IntegraMent

Presenting Author: Fabian Streit

Liz Rietschel (2,3), Josef Frank (1), Stephanie H. Witt (1), Tina Binz (4), Andreas Forstner (5,6), CORtisolNETwork (CORNET) Consortium; Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium (PGC), Thomas G. Schulze (1,7,8,9,10), Markus Nöthen (5,6), Nicholas Martin (3), Marcella Rietschel (1)

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Hair cortisol concentration (HCC) is a measure of long-term hypothalamus-pituitary-adrenal (HPA) axis activity. Previous research has suggested an association between HCC and psychological variables, and first studies of inter-individual variance in HCC have implicated genetic factors. The aims of the present twin study were to assess the heritability of HCC and to estimate the phenotypic and genetic correlation between HPA axis activity and the psychological variables perceived stress, depressive symptoms, and neuroticism. This was investigated using formal genetic twin models and molecular genetic methods, i.e. polygenic risk scores (PRS). HCC was assessed in 671 adolescents and young adults including 115 monozygotic and 183 dizygotic twin-pairs. In 432 subjects with genotyping data available, PRS scores for plasma cortisol, major depression, and neuroticism were calculated using data from large genome wide association studies. The twin model revealed a heritability estimate for HCC of 72%. No significant phenotypic or genetic correlations between HCC and the three psychological variables of interest were observed. PRS did not explain variance in HCC. The present data suggest that HCC is highly heritable. However, the data do not support a strong biological link between HCC and any of the investigated psychological variables.

Schizophrenia-associated protein ZNF804A identified as a repressor of STAT2 immune response.

IntegraMent

Presenting Author: Konrad Klockmeier

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Schizophrenia is a complex neuropsychiatric disorder and represents a significant public health problem. Huge efforts have been made to identify causative genes for schizophrenia in the recent past by GWAS, CNV and exome sequencing studies. One gene repeatedly associated with SCZ through GWAS studies is ZNF804A. ZNF804A is a zinc finger protein whose function remains largely unknown. Most proteins interact with other proteins to fulfill their functions; therefore, the analysis of protein-protein interaction partners is a valid approach to annotate proteins. We used the yeast-2-hybrid system to screen seven ZNF804A constructs against a library of over 17,000 proteins and were able to identify 18 previously unknown ZNF804A interactors. We validated these interactions using two recently established methods: DULIP (dual luminescence immunoprecipitation, Trepte et al. 2015) and BRET, both in mammalian cells, with an overall validation rate of 67%. The most promising interaction partner of ZNF804A was STAT2. STAT2 is a key mediator of the interferon α/β-mediated cellular immune response and induces an antiviral state. Confocal microscopy identified ZNF804A to co-migrate with STAT2 into the nucleus after INFα induction, both in HEK cells and in neurons. ISRE reporter assays as well as qPCR quantification of OAS1 and 2, IFIT1 and 3, as well as RASD2 indicate a potential repressive role of ZNF804A on STAT2-mediated target expression. The implication of ZNF804A as a repressor of the cellular immune response increases our understanding of schizophrenia and could leads to new approaches for drug development.

Common genetic variants associated with personality dimensions in the Heidelberg Cohort Study of the Elderly (HeiDE): an update

IntegraMent

Presenting Author: Urs Heilbronner

Urs Heilbronner (1), Till F. M. Andlauer (2), Sergi Papiol (1), Monika Budde (1), Jana Strohmaier (3), Fabian Streit (3), Josef Frank (3), Manfred Amelang (4), Til Stürmer (5), Bertram Müller-Myhsok (2), Marcella Rietschel (3) and Thomas G. Schulze (1)

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HeiDE is a longitudinal study that started in the 1990s and, at baseline, assessed an array of personality tests in 5,114 individuals. Five latent personality dimensions ("The Heidelberg Five"), were identified and interpreted as emotional lability (ELAB), lack of behavioral control (LBCN), type-A-behavior (TYAB), locus of control over disease (LOCC), and psychoticism (PSYC). At follow-up, a subset of responding participants (n=2,734) were genotyped on SNP arrays. We conducted five initial GWAS, analyzing common SNPs underlying "The Heidelberg Five" with factor scores as phenotypes. For ELAB, we observed a locus that was genome-wide significant. Recently, genome-wide data from a second sample of the HeiDE study became available and we have now jointly analyzed both samples and combined results using meta-analysis (n=2,387 and n=881; post-QC). We have also estimated SNP-based heritabilities of and genetic correlations between "The Heidelberg Five".

Common variants (MAF ≥ 0.01) were imputed using the 1000 Genomes Phase 3 reference panel. Data were analyzed using PLINK 1.07 with sex, age and the first four ancestry principal components as covariates. METAL was used for fixed-effects meta-analysis. GCTA was used to calculate heritability estimates and genetic correlations. The previously reported association of SNP rs79136259 with ELAB did not replicate. For TYAB, an InDel variant on chromosome 8 (rs58535027), reached genome-wide significance in the meta-analysis. No other genome-wide significant associations were found. SNP-based heritability estimates of the joint genotype data were: 28.8% (ELAB; FDR p=0.047), 27.3% (LBCN; FDR p=0.047), 8.4% (TYAB; FDR p=0.269), 8.4% (LOCC; FDR p=0.269) and 23.6% (PSYC; FDR p=0.047). None of the genetic correlations reached nominal significance. Heritability of some personality traits can thus be demonstrated using common SNPs and the phenotypic orthogonality of the latent personality traits appears to be mirrored on the genomic level.

Finding schizophrenia related pathways

IntegraMent

Presenting Author: Karolina Worf

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Schizophrenia is a complex psychiatric disorder with a life-time risk of ~1% and a high estimated heritability of approximately 80%. Several family and association studies of schizophrenia discover new disease-causing genetic variants and/or their altered genes. Hence, a large number of genes is already associated with the disease, but their functional complexity and variety restrains our understanding of the underlying molecular pathways. To that end, we are trying to identify pathways using three complementary strategies: We analyse 1) gene sets of directly schizophrenia associated genes, 2) a nearest neighbours-, and 3) a weighted nearest neighbours approach of schizophrenia associated genes. As input, we use a list of schizophrenia-associated genes extracted from literature, a list of rare variants found in index patients with severe forms of schizophrenia, and a list of co-segregated variants identified in multiply affected schizophrenia families. Then, we first collect data from the publicly available pathway databases KEGG, Reactome, and WikiPathways, and perform a gene set enrichment analysis by means of Fisher's exact test with Bonferroni correction. Second, we use the PPI-networks HPRD and STRING, onto which we map the schizophrenia-related genes, and take their nearest neighbours to again do a gene set enrichment analysis. Finally, we use weighted nearest neighbours, where we extend the gene signal through the edges of the network through a network smoothing algorithm, and then perform a ranged gene set analysis method. For all three strategies, we check if we can find the same significantly enriched pathways. In the process, we especially identified signaling pathways to be most frequently associated to schizophrenia-related genes. For verification, we will now compare our findings with the results of a gene set enrichment analysis using random generated data sets. Thus, we hope to shed some lights into the pathogenesis of schizophrenia.

The effects of a bipolar disorder associated SNP on ADCY2 protein function and mouse behavior

IntegraMent

Presenting Author: Paromita Sen

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Bipolar Disorder (BD) is a multifactorial disease with both genetic and environmental factors contributing to it. The single nucleotide polymorphism (SNP): rs13166360 located at 5p15.31 was identified to be one of the polymorphisms that is genome wide significant for BD. This SNP is a deviation from the major allele G to T (minor allele) that encodes a Valine to Leucine missense codon in adenylate cyclase 2 (ADCY2). This polymorphism is speculated to cause functional variation in the protein that may affect BD susceptibility. However, the precise effect of this polymorphism on protein function and its influence on BD susceptibility is still not known. In order to study the differences in function of the major and the minor allele of ADCY2, we cloned the two variants of ADCY2 into expression vectors and will transfect cell lines with low level of endogenous ADCY. We aim to use cAMP assays to compare the differences in activity of the transiently overexpressed ADCY2 variants. Currently, we are optimizing two different cAMP assays: one that measures differences in total cAMP production between the two variants, and another that studies the differences in the dynamics of cAMP production. To address the function of ADCY2 in vivo we generated a V151L mouse line mimicking this desired polymorphism in mice using the CRISPR/Cas9 system. In order to investigate the influence of this polymorphism on BD susceptibility, we screened for differences in anxiety, locomotion, stress coping behaviour, social interaction and fear memory under basal housing conditions. In the future, we will study the differences in these behaviours after exposure to chronic social stress using the chronic social defeat paradigm.

SYSKON. Re-Configuration of Health and Disease. Ethical, Psycho-Social, Legal and Health-Economic Challenges of Systems Medicine: The Case of Hereditary Breast Cancer.

SYSKON

Presenting Author: Friedhelm Meier

Autoren: Friedhelm Meier (1), Kerstin Rhiem (2), Julia Dick (2), Anke Harney (3), Silke Neusser (4), Anja Neumann (4), Jürgen Wasem (4), Stefan Huster (3), Rita Schmutzler (2), Peter Dabrock (1)

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Background: Referring to hereditary breast cancer as a paradigmatic case, SYSKON investigates challenges and chances of systems medicine, consequences for clinical care in particular and the healthcare system in general. The overall question is, to what extend BRCA1/2 mutation carriers in particular and genetic persons at risk should be integrated into the healthcare system and/or have entitlement to preventive measures.

Structure: SYSKON comprises five subprojects: Administration (SP1, Erlangen), Ethics (SP2, Erlangen), Psycho-Social (SP3, Cologne), Law (SP4, Bochum) and Health Economics (SP5, Duisburg-Essen).

Aims: SYSKON investigated the challenges of risk communication and the crucial social factors influencing the decision making process (psycho-social SP). Further, SYSKON showed that the entitlement of BRCA1/2 mutation carriers isn't clearly regulated. This unregulated situation implies legal uncertainty for patients and a need for clarification (legal SP). The health-economic SP pointed out the budget impact of a regulated entitlement for BRCA1/2 mutation carriers to the healthcare system. SYSKON has developed the 'heatlhy sick'-model as a potential framework for the integration of BRCA1/2 mutation carriers in particular and genetic persons at risks in general into the healthcare system (ethical SP). The composition of all findings builds the basis of the governance perspective. This document recommends a regulated entitlement of BRCA1/2 mutation carriers, explains task-related criteria for decision makers and gives a strong groundwork for an adequate integration of genetic persons at risks into the healthcare system in general.

Public activities: To discuss the extraordinary relevant topic at the interface of science and society SYSKON participated and held various public events (e.g. panel discussions) and lectures.

Toward causal mechanism in Systems Neuroscience: Implications for Primate Welfare

Presenting Author: Antonella Tramacere

Tramacere A., Iriki A.

Lichtenberg-Kolleg/The Göttingen Institute for Advanced Study & The German Primate Center/Leibniz Institute for Primate Research, Georg-August-Universität Göttingen

Progresses in molecular biology and neuroscience are contributing to uncovering the biological bases of various cognitive functions and psychiatric disorders. Yet, because of both technical and ethical challenges (i.e., respectively the integration of a huge number of heterogeneous data and the limits of biomedical experimentation) these findings have not been translated in causal mechanisms and effective therapies for diseases. We emphasize the importance of Research domain criteria (RDoC) - a heuristic framework for the incorporation of neurogenetics, social and behavioral neuroscience and psychiatry, for studying the primate brain, and suggest a new mind-set in primate experimentation within the boundaries of animal welfare regulations. Specifically, we list the advantages of uncovering the interactions between genes and socio-environmental factors in the emergence of mental traits and psychiatric disorders, and propose the establishment of an open discipline of systems neuroscience, which can make use of up-to-date investigative and statistical technologies. Systems neuroscience may be conducted by implementing and harmonizing experimental and interpretative practices with ethical guidelines (i.e., 3Rs) that regulate 1) management of natural parks with natural and eventually genetically modified primate populations living in naturalistic settings; 2) establishment of eco-labs for extensive and non-invasive investigations in the wild, 3) hotel space and technologies which remotely collect and dislocate information regarding primates geographically located elsewhere, plus 4) systematic and continuous comparison between non-human and human research.

e:Med
SYSTEMS MEDICINE

Poster Presentations

Modelling in Systems Medicine

Application of a 3D hybrid multi-scale model for simulation of growth of hepatocellular carcinoma (HCC) and therapies

Multiscale HCC

Presenting Author: Matthias Reuss

M. Reuss1), T. Yoshi1), A. Lapin1), Perfahl, H.1), Bitzer, M.2), Horger, M.2), Malek, N.2), Pichler, B.2)

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In the HCC project we use a multiscale hybrid discrete-continuum model (ref.1) to simulate angiogenesis and vascular tumor growth of hepatocellular carcinoma. The model is based on a cellular automaton approach and couples intracellular processes, active cell movement, cell-cell interaction, extracellular diffusion, and a dynamically evolving vascular network. A successful application of this general model for analysis of the special issues of hepatocellular carcinoma requires (1) modifications and extensions to involve the very special and complex architecture and structural morphology of the liver and (2) expansion of modeling modules required for the essential model verification with imaging data from patients and animal models. Model based data for perfusion CT are generated from a rigorous simulation of the integrated vascular and transvascular flow coupled to the increase of tumor pressure caused by flow through the interstitium. For use of FDG-PET data further extensions of the model regarding the glucose balance are required. The second part of the lecture deals with the application of the 3D hybrid multiscale model for simulations of therapies. After further refinement of the mathematical model it is possible to simulate the transarterial chemoembolisation (TACE) also in combination with sorafenib treatment. Perfahl, H., Byrne, H.M., Chen, T., Estrella, V., Alarcon, T., Lapin, A., Gatenby, R.A., Gillies, R.J., Maini, P.K., Reuss, M., Owen, M.R. (2011) Multiscal Modelling of Vascular Tumour Growth in 3D, PLoS one, Vol. 6, e14790.

Using Mixed Integer Linear Programming to identify regulators of telomerase expression

CancerTelSys

Presenting Author: Alexandra Poos

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Telomeres are nucleoprotein structures at the ends of eukaryotic chromosomes protecting them against fusion, degradation, and unwanted double-strand break repair activation. In somatic cells, they shorten gradually with each cell division eventually triggering replicative senescence or apoptosis, thereby preventing unlimited proliferation. Cancer cells overcome this restriction frequently by maintaining their telomeres by re-expressing the reverse transcriptase telomerase, which normally is only active in stem cells and not expressed in most somatic cells. Understanding the mechanisms that maintain telomere length has substantial medical implications, in particular for ageing and carcinogenesis. Here, we integrated Mixed Integer Linear Programming models into a comparative machine learning based approach to identify regulatory interactions that best explain the discrepancy of telomerase transcript levels. Initially, we applied our method on yeast deletion strain data with aberrant telomere length compared to control samples. We uncovered novel regulators of telomerase expression, several of which affect histone levels or modifications (Poos et al., 2016, Nucleic Acids Research). In the present study, we employed our method to explore the regulation of the telomerase in cancer cells and to identify specific transcriptional regulators of the human telomerase gene hTERT in different cancer types. We used RNA-Seq data from The Cancer Genome Atlas (TCGA) and regulator binding information from different databases (e.g. MetaCore, Chea, Encode) and identified PITX1 as a prostate cancer specific hTERT regulator. PITX1 was linked into a regulatory network and further validated in the clinics as a good prognostic marker for prostate cancer. The computational approach presented here identified central regulators of the telomerase in prostate cancer paving the way for targeted therapy.

CYP3A5 expression in PDAC cells results in tumor niches protected from cytotoxic drugs

PANC-STRAT

Presenting Author: Stefan Kallenberger

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive cancers with poor prognosis. Chemotherapy mostly fails from primary and acquired resistance of tumor cells. Recently, CYP3A5 overexpression was discovered in a subset of PDACs leading to metabolism and inactivation of tyrosine kinase inhibitors (TKIs) and paclitaxel. The local detoxification and inactivation of drug likely results in different distribution profiles which have important consequences for drug dosing in a clinical setting. By mathematical modeling and experiments, we aim to characterize consequences of CYP3A5 overexpression towards chemotherapy resistance. Immunostained sections of tumors showed heterogeneous CYP3A5 expression. Therefore, we hypothesized that CYP3A5 overexpressing cells also protect surrounding cells, which do not overexpress CYP3A5, by drug degradation. Using reaction-diffusion models, we simulated drug diffusion and degradation, and CYP3A5 expression in 3D cell cultures. By simulating enzyme induction in response to drug exposure, CYP3A5 expression kinetics observed in different PDAC subtypes shall be reflected. Modeling predicted that CYP3A5 expressing cells cause spatially confined drug exposed tissue regions in which drug concentrations reach steady states. At given fractions of CYP3A5-expressing cells, dimensions of tumor regions that are effectively protected from drugs were predicted. Simulations were conducted to plan experiments in 3D co-cultures of CYP3A5-overexpressing and CYP3A5 negative cells. Taken together, we could correlate the experimentally observed heterogeneous expression of CYP3A5 in PDACs with the ability of protecting surrounding cancer cells not expressing CYP3A5. In the next step, cytotoxicities of erlotinib and paclitaxel, dependent on drug concentrations and exposure times, will be characterized in selected patient-derived cell lines of different PDAC subtypes.

The Impact of Cellular Composition on Stratification of Pancreatic Ductal Adenocarcinoma

PANC-STRAT

Presenting Author: Jing Yang

Jing Yang1, Elisa Espinet 3,4, Zuguang Gu1, Corinna Klein3,4, Vanessa Vogel3,4, Alexander Muckenhuber5, Wilko Weichert5, Thilo Hackert6, Nathalia A. Giese6, Oliver Strobel6, Martin Sprick3,4, Andreas Trumpp3,4, Roland Eils1,2, Tobias Bauer1,2, Matthias Schlesner1,7

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A common feature of pancreatic ductal adenocarcinoma (PDAC) is the presence of large amounts of non-cancerous cells in the tumor microenvironment. The low tumor cell content of the tumor tissue hampers genetic analysis and might strongly bias the stratification of tumor samples based on gene expression data. PDAC subclasses found in bulk tumor expression data might not necessarily reflect tumor cell subtypes but rather tumor cell composition, as some of the signature genes are not specific of cancerous cells. We are applying deconvolution method to RNA-seq data from PDAC samples to estimate the proportion of malignant epithelial, immune, fibroblast, endothelial and normal epithelial cells, which are the major cell types in PDAC. Our study is built on the assumption that the expression signal of a gene in a complex sample is a convolution of the expression of that gene by all present cell types. We used pure transcriptomes of different cell types sorted from human PDAC and normal pancreatic tissue to identify representative and stably expressed genes as signature genes for each cell type and then performed deconvolution of RNA-seq data from bulk PDAC tissue using CIBERSORT. Our results for the estimated proportion of epithelial, immune and fibroblast cells are in well agreement with those from previously published methods and we show that the estimated proportions of malignant cells correlate with the tumor purities inferred from exome-seq data of the same cohort. In contrast to previous studies we are additionally able to distinguish normal and malignant epithelial cells, and we can also estimate the proportion of endothelial cells in the tissue. We show that gene expression of normal epithelial cells and immune cells has a strong influence on stratification analysis. Hence, the information about cellular composition shows extremely useful for a more comprehensive analysis of expression data originated from bulk tumor samples.

Spatial Gene Expression in Liver – Regulation by Autocrine and Paracrine Wnt/β-Catenin Signalling

SYSMED-NB

Presenting Author: Uwe Benary

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Cells coordinate their function within highly organised tissues such as liver via secreted factors. Aberrant secretion by cancer cells may affect this communication. Hepatocytes, the major liver cell type, secrete Dickkopf (Dkk), which inhibits Wnt/β-catenin signalling in an autocrine and paracrine manner. Our mathematical modelling approach describes hepatic gene expression along the porto-central (PC) axis under wild-type conditions as well as in the presence of carcinogenic pathway mutations. We explore the impact of different gene regulatory mechanisms such as activation, inhibition, and incoherent feedforward loops (iFFL). An APC concentration gradient is modelled along the PC axis as observed in liver. Our simulations show that a combination of cooperative activation and transcriptional feedback can establish region-specific, locally confined gene expression, explaining the zonation of liver functions. To study autocrine and paracrine regulation by Dkk, we extended our model by a competition mechanism of Dkk and Wnt at receptor level, and Dkk diffusion between the hepatocytes along the PC axis. Simulations of pathway-activating mutations show that already a single mutant cell increases overall Dkk concentration. The influence of a mutant cell on gene expression of the wild-type hepatocytes is however limited in magnitude and restricted to cells in close proximity. Taken together, we show that (i) the combination of specific gene regulatory mechanisms with a gradient of APC is sufficient to generate spatially distinct gene expression profiles as observed in experiments, and (ii) the combination of inter- and intracellular processes allow wild-type hepatocytes to largely maintain their gene expression in the presence of individual mutant cells. Benary, Kofahl, et al. Front Physiol. 2013. Hartung, et al. BMC Syst. Biol., accepted for publication.

Computational Modelling of MYC-dependent Gene Regulation in Cancer Cells

SYSMED-NB

Presenting Author: Jana Wolf

Uwe Benary, Jana Wolf

Max Delbrück Center for Molecular Medicine in the Helmholtz Association

Human MYC is a transcription factor that plays a major role in the regulation of cell proliferation. Upregulation of MYC expression contributes to cancer development and is associated with tumour aggressiveness. Several studies suggest that MYC binds to a specific DNA motif termed enhancer box (E-box), with a consensus sequence of CACGTG, and thereby regulates the transcription of specific target genes. However, recent chromatin-immunoprecipitation (ChIP) and ChIP-sequencing experiments demonstrate that MYC binds to almost all sites within open chromatin, independent of E-boxes. Despite this global DNA binding, MYC-dependent tumours seem to harbour a specific set of up- and down-regulated MYC target genes. Several hypotheses have been proposed to explain cell type specific MYC target gene expression despite genome wide DNA binding. One model suggests that MYC globally enhances transcription and specific gene expression arises indirectly due to regulatory feedback loops. An alternative hypothesis suggests that a large portion of MYC binding to DNA is non-productive resulting in a specific set of regulated genes. We suggest that specific gene expression profiles arise since target gene promoters differ in their affinity for MYC. Our computational modelling approach in combination with extensive experimental data demonstrates that differences in MYC-DNA-binding affinity are sufficient to explain the distinct promoter occupancies observed in ChIP-sequencing experiments. Affinities estimated from our experimental data allow for a stratification of distinct MYC-regulated biological processes at different MYC concentrations. We suggest that interactions between MYC and promoter-bound factors may increase promoter affinities, indicating a molecular mechanism of context-specific modulation of MYC-dependent transcriptional responses of individual genes. Lorenzin, et al. DOI: 10.7554/eLife.15161 Benary, et al. DOI: 10.18547/gcb.2017.vol3.iss2.e54

Modeling the MYCN-mediated effects on sugar metabolism

SYSMED-NB

Presenting Author: Mareike Simon

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MYCN is a driving oncogene in many cancer types including neuroblastoma (NB), a solid tumor of early childhood. Prognosis of NB harboring tumor-specific amplification of the MYCN oncogene is associated with poor patient outcome. Previous studies suggested a MYCN-induced shift between usage of glycolysis and oxidative phosphorylation in cancer cells, but mechanistic data are largely lacking. To gain a deeper understanding of the impact of MYCN on the central carbon metabolism in neuroblastoma, we generated neuroblastoma cells with inducible expression of MYCN. Using these cells, we characterized the biological effects of MYCN induction on expression of target genes and on enzymatic activity of putative MYCN targets in nutrient-rich conditions or under starvation. These results served to investigate MYCN-driven regulation metabolic activity in the framework of mathematical modeling with the aim to develop a computational model that represents the central carbon metabolism depending on nutrient availability and MYCN status. Sensitivity analysis will be performed in order to evaluate the influence of the different parameters on the behavior of the system and to identify possible drug targets.

Modeling transcription factor activity based on target gene expression

MILES

Presenting Author: Janis Neumann

Janis Neumann1,2, Andreas Beyer1,2, Mathieu Clément-Ziza1,2

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Transcription factors (TFs) bind to the DNA to modulate the expression of their target genes. While the mechanisms of action of TFs have been extensively studied, it remains hard to quantify their specific activity. The activity of a TF cannot directly be measured at high-throughput. It has been proposed to model the activity of TFs using the effects they have on the expression of their target genes. Existing strategies often linearly regress gene expression levels on the probability of each TF to control a given gene. Several variations of this concept have been developed. However, a systematic validation of the approach in general and individual methods in particular have not been carried out. To this end, we have designed a framework that allows to assess the biological relevance and the performance of the different methods modeling the TF activity. At its core, it makes use of biological data in which a priori knowledge of the activity of a transcription factor exists – namely, TF knockdowns. We rank the methods based on their ability to identify the TF that was knocked down based on expression changes. Expression data derived form mouse embryonic stem cells and a human lymphoblastoid cell line was exploited in this framework to assess the performance of both published and novel methods. These methods include different ways of determining TF targets, data processing approaches, and modeling methods. All possible combinations of methods were tested to both find optimal strategies and thoroughly investigate the performance of each method. This work revealed important differences in how well individual transcription factors can be modeled. Moreover, several strategies that improve upon previously published modeling methods could be identified. The TF activity modeling methods we have developed are currently applied to tumor data to explore lineage-specific TF activity profiles.

Using mechanistic models to unravel the role of ErbB signaling in resistance to antibody-based therapies in gastric cancer

SYS-Stomach

Presenting Author: Elba Raimundez Alvarez

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Background: Alterations in the ErbB receptor family and ErbB-related signaling pathways are frequently observed in gastric cancer (GC). Novel drugs targeting members of the ErbB family have shown mixed success in clinical trials. Trastuzumab, a ErbB2 antibody, has been approved for GC treatment whereas cetuximab, a ErbB1 antibody, has failed in a phase III clinical trial. Thus, understanding the connection between the molecular mechanisms and the treatment success of these therapies for GC and identification of predictive biomarkers for patient stratification is highly valuable.

Methods: We developed a mechanistic ordinary differential equation model for the ErbB, ERK and AKT signaling pathways. This model describes the intracellular signal transduction of the cetuximab responder cell line, MKN1, and non-responder cell line, Hs746T; and its link to phenotypic properties, such as cell motility. Specific genetic features, time-resolved measurements and dose-response curves for these individual GC cell lines are described in the model. A large amount of molecular and phenotypic data collected under a wide range of different experimental conditions is available to train the model, for which we used the Matlab toolbox Data2Dynamics. Model selection was done to identify the most important differences between the responder and non-responder cell lines.

Results: Our model-based analysis showed the importance of the mutation status of the MET receptor in the Hs746T cell line and the role of PI3K mutations and receptor internalization. The model provides information on the relevance of individual molecular alterations and establishes the link between the signaling state of the cell and the cellular phenotype. Predictions for new experimental conditions were validated highlighting the value and predictive power of the model. Next, this model will be extended to include afatinib treatment to provide additional information on relevant molecular properties of the cell lines.

Combinatorial blockade of ERBB receptors in HER2 low breast cancer: a therapeutic approach.

HER2Low

Presenting Author: Mireia Berdiel-Acer

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Large number of breast cancer patients clinically classified as HER2 negative, show low/moderate levels of HER2 along with other ERBB receptors. Concomitant blockade of EGFR, ERBB2 and ERBB3 with specific therapeutic antibodies (cetuximab, trastuzumab/pertuzumab and lumretuzumab, respectively) appears as a beneficial approach to improve survival of patients who have failed to previous treatment strategies. Additionally, ERBB3 expression has been reported as a trastuzumab resistance mechanism in HER2 positive subtypes. We have confirmed a specific pattern of ERBB receptors expression in different breast cancer subtypes. Individual and combined blockade of the receptors with therapeutic antibodies has been tested in vitro using a metabolic viability assay (Cell Titer Glo). All four therapeutic antibodies bind to the respective extracellular domains inhibiting downstream signaling pathways. Response to individual treatment is cell dependent and correlates with EGFR expression in the triple negative MDA-MB-468 but not in luminal T47D and MCF7 cancer cell lines. Response of T47D cells to lumretuzumab is higher when combined with pertuzumab or trastuzumab, suggesting ERBB2/ERBB3 dimer as the most relevant one upon pathway activation with ectopic NRG1 (the only ligand for ERBB3). Exposure of MDA-MB468 cells to cetuximab induces ERBB3 expression and increases its sensitivity to cetuximab when combined. As well as, in the HER2+ BT474 cancer cell line resistant to trastuzumab, higher levels of ERBB3 also make cells more sensitive to alternative anti-ERBB therapies. Although treatment of HER2 overexpressing breast tumors has been successful, targeting other ERBB members in a HER2 moderate/low scenario seems to be a promising approach in combinatorial therapies; even in resistant cell lines. Thus, better characterization of ERBB network should help to pave the way for a more personalized treatment of HER2 low breast cancer.

HER2Low: Targeting the ERBB-module in HER2-low breast cancer; Mathematical modeling of response towards drugs targeting HER2, EGFR and ERBB3 to personalize breast cancer treatment

HER2Low

Presenting Author: Daniela Berg and Eileen Reinz

Daniela Berg (1), Eileen Reinz (1), Jens Timmer (2), Daniel Kaschek (2), Max Hasmann (3), Tim Beißbarth (4), Annalen Bleckmann (4), Tobias Pukrop (4), Andreas Schneeweiss (5), Martina Vetter (6), Niels de Jonge (7), Stefan Wiemann (1), Ulrike Korf† (1)

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Breast cancer is the most common cancer in women worldwide with over 1.5 million new cases diagnosed each year. About 70-80% of primary breast tumors show low or no detectable expression of HER2, however, other members of the ERBB family of receptor tyrosine kinases (RTK), EGFR and ERBB3, are frequently expressed as potent drivers of tumor progression and of metastasis, particularly in relapsed disease. To better understand the complex interplay of RTKs and their downstream signaling particularly in breast cancer expressing HER2 at low to moderate levels the HER2Low consortium analyzes therapeutic antibodies targeting EGFR, HER2 and ERBB3. Initially we studied established cell line models in order to employ a systems medicine approach towards efficient inhibition of EGFR/ERBB receptors, signaling, and cancer-related phenotypes. In our project we focus on drug response towards Cetuximab, Trastuzumab/Pertuzumab, and Lumretuzumab treatment inhibiting EGFR, HER2 and ERBB3, respectively. Using Reverse Phase Protein Array technology and >100 specific antibodies, abundance and phosphorylation states of downstream signaling molecules in an extended MAPK/AKT-network were quantified in response to ligands (EGF, HRG1ß, AREG, TGFα, BTC) and upon inhibition of receptors. Subsequently mathematical models were built and compared with quantitative data obtained from the analysis of clinical samples to validate patterns of drug response predicting combinatorial inhibition of receptors. Additionally, we quantified the levels of all ligands in the supernatants to learn about 1. ligand internalization/degradation and 2. uptake/secretion of other ligands. The latter should uncover interactions of tumor cells within their microenvironment. Our final aim is to predict efficient drug combinations to drive personalized therapy decisions based on the proteomic profile of a tumor.

Analyzing molecular changes during drug resistance of melanoma using a Dynamic Bayesian Network approach

Melanoma sensitivity

Presenting Author: Philippe Lucarelli

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Despite remarkable scientific and clinical efforts in melanoma research, the incidence of malignant melanoma strongly increased over the last decades. While metastatic melanoma is often characterized by mutation of the kinase BRAF, the large number of different mutations represent the biggest challenge in our understanding of the disease. These mutations strongly increase the aggressiveness of the tumor offering a poor prognosis for the patient. The response to conventional therapeutic treatment usually lasts for a few months only, until drug resistance occurs, leading to tumor relapse which often coincides with increased proliferation and migration rates. The goal of this study is to identify the critical mechanisms leading to drug resistance in A375 melanoma cell lines. For an in-depth analysis of signal transduction pathways that might confer therapy resistance, we apply a systems biology approach based on a Dynamic Bayesian Network (DBN), which integrates steady-state time-course data into a mathematical model, to identify the optimal drug combination for a successful treatment. A mathematical model analyzing the crosstalk interactions for the death ligand TRAIL-induced apoptotic signal transduction has been established and refined based on newly acquired experimental time-course data. We employ a DBN modeling approach to analyze the molecular interactions and regulations among signaling molecules with minimal parameterization. This modeling approach allowed us to identify cell type specific reactions. Currently, we were able to dissect the critical crosstalk mechanisms of the TRAIL signal transduction pathways by DBN modelling and are able to show the influence of the different pathways for each steady-state. In the next step, we aim to identify which drug combinations render resistant melanoma cells sensitive towards apoptotic cell death. The newly identified targets and combinations will be validated in selected melanoma in vitro models.

Synergistic changes in global gene expression and cellular metabolism by factors of the microenvironment.

MMML-Demonstrators

Presenting Author: D. Kube

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There is increasing evidence that apart from aberrant activated protooncogenes as for example MYC, the tumor microenvironment and host immunity play an important role in lymphoma. Myc-tranformed cells are characterized by an increased glucose and glutamine utilization often accompanied by changes in the gene expression of key enzymes of metabolic pathways. The aim of the study was to characterize the effects of factors of the microenvironment of lymphoma onto the global gene expression and cellular metabolism in the context of high or low Myc expression. A corresponding B cell line was used where the expression of Myc can be switched off and on. This cell line was stimulated by defined sets of single B cell specific stimuli and their combinations. RNA-Seq analysis revealed a global shift in gene expression including genes important for glycolysis and glutaminolysis. Using NMR/mass-spec changes in the metabolism of amino acids and metabolites of the glycolysis and the citric acid cycle are observed. A combination of microenvironmental factors affecting the STAT/NF-kB pathway in Myclow conditions are activating gene expression of genes important for glycolysis and glutaminolysis in a synergistic way as shown by regression analysis. The same was observed for most of the corresponding metabolites. By 13C- and 15N-tracing, metabolite rescue experiments, and oxygen measurements, we demonstrate that the aminotransferase GOT2 is a metabolic hub providing Asp and nucleotides to cells with activated (P493-6) or aberrant Jak/STAT and NF-κB signaling (OCI-Ly3, L428). A model of GOT2 transcriptional regulation is proposed, in which the cooperative phosphorylation of STAT3 and direct joint binding of STAT3 and p65/NF-κB to the proximal GOT2 promoter are important. Furthermore, high aberrant GOT2 expression is prognostic in diffuse large B-cell lymphoma. Consequently, GOT2 may represent a promising target for targeted cancer therapy.

Predicting the influence of combination therapies in signaling networks

MMML-Demonstrators

Presenting Author: Maren Sitte

Dieter Kube (Departement of Immunology and experimental Oncology, University Medical Center Göttingen) , Nils Blüthgen (Departement of Pathology, Charité – University Medical Center Berlin), Rainer Spang (Institute of Functional Genomics, University of Regensburg), Tim Beissbarth (Department of Medical Statistics, University Medical Center Göttingen)

The consortium named “Molecular Mechanisms in Malignant Lymphomas - Demonstrators of Personalized Medicine” compound of research groups of biologists, bioinformaticians and doctors propose to develop prognostic and diagnostic platforms that guide treatment decisions and that support the process of therapeutic target identification in diffuse large B-cell lymphomas (DLBCL). The focus lies on the DLBCL microenvironment as prognostic relevance, which is the foundation of the diagnostic platforms the consortium will establish. The communication of the cell microenvironment with the tumour cells will be the target for the novel therapeutic strategies the consortium wants to investigate. In our subproject, we aim to investigate hybrid-models, which will integrate signalling data with existing gene expression data to predict how lymphomas translate signalling stimuli in expression phenotypes. For this approach we will integrate pathway knowledge and experimental data and implement previously developed network reconstruction methodology. These existing approaches as Deterministic Effects Propagation Networks (Bender et al., 2011) and Nested Effects Models (Fröhlich et al., 2008; Markowetz et al., 2005) are based on Bayesian networks. This is the ground line of my research and shall be adapted, so that measurements from proteomic experiments and prior pathway knowledge can be combined.

Implementing a multilayer framework for pathway data integration, analysis and visualization

MultiPath

Presenting Author: Zaynab Hammoud

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Personalized medicine promises an improved health care by customizing the treatment according to patient needs[3]. The methods to analyse data, model knowledge and store interpretable results vary widely. A common approach is to use networks for modelling and organizing this information. Network theory has been used for many years in the modelling and analysis of complex systems, as epidemiology, biology and biomedicine [1]. As the data evolves and becomes more heterogeneous, monoplex networks become an oversimplification of the corresponding systems[3]. This imposes a need to go beyond traditional networks into a richer framework capable of hosting objects and relations of different scales[4], called Multilayered Network. These complex networks have contributed in many contexts and fields [1], although they have been rarely exploited in the investigation of biological networks, where they are very applicable.[2] In order to fill this gap, we aim to implement a multilayer framework that can be applicable in various domains, especially in the field of pathway modelling. Our idea is to integrate pathways and their related knowledge into a multilayer model, where each layer represents one of their elements. In this poster, we give an overview of the various models of multilayered networks, then we describe the model we are building, and the workflow of implementing it into an R package as well as the future plan. References 1. Kivelä et al., “Multilayer Networks.”. Journal of Complex Networks (2014) 2, 203–271 2. De Domenico, Porter, and Arenas, “MuxViz: a tool for multilayer analysis and visualization of networks.”. Journal of Complex Networks (2015) 3, 159–176 3. Boccaletti et al., “The Structure and Dynamics of Multilayer Networks.”. Physics Reports 544, 1 (2014) 4. Traxl, Boers, and Kurths, “Deep Graphs - a General Framework to Represent and Analyze Heterogeneous Complex Systems across Scales.”. Chaos 26, 065303 (2016)

A biomathematical model of human erythropoiesis and iron metabolism

HaematoOPT

Presenting Author: Sibylle Schirm

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A frequent complication of renal disease is anemia and iron deficiency. Anemia therapy of these patients requires both, EPO and iron medication. However, excessive iron medication can cause iron overload. It is a challenge of anemia treatment under chronic kidney disease to control hemoglobin levels of these patients in a desired range. We combined our previously established model of human erythropoiesis including comprehensive pharmacokinetic models of EPO application with a newly developed model of iron metabolism including iron supplementation. Equations were derived by translating known biological mechanisms into ordinary differential equations. The model can explain time courses of erythrocytes, reticulocytes, hemoglobin, hematocrit, red blood cells, EPO, serum iron, ferritin, transferrin saturation, and transferrin under a variety of scenarios including EPO and iron application into healthy volunteers. Unknown model parameters were determined by fitting the predictions of the model to time series data from literature. Following our ultimate goal of establishing a model of anaemia treatment in chronic kidney disease, we aim at translating our model to this pathologic condition in the near future.

A mathematical model for predicting the dynamics of tumor-reactive lymphocytes in murine melanoma model

TIL-REP

Presenting Author: Lena M. Appel

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Immunotherapeutic approaches have become a therapeutic option for several cancers. Still, the underlying mechanisms of the antitumor immune response are poorly understood which is reflected in the unpredictability of the individual patient's response to these treatments.

Aim: Understand underlying mechanisms of the antitumor T cell response and the effect of immunotherapeutic treatment with anti-CD40 in the murine melanoma mouse model with the help of a mathematical model.

Experimental setting: B16-OVA murine melanoma model with and without anti CD40 treatment. Inoculation of tumor about 20 days prior to the transfer of naïve OT-I T cells which recognize an OVA-derived peptide. Monitor their proliferation with the cell dye Carboxyfluorescein Diacetate Succinimidyl Ester (CFSE) and measure cell numbers in all relevant compartments (tumor, blood, draining and non-draining lymph nodes, spleen).

Results/Highlights:

- proliferative activity of the transferred OT-I T cells in the draining lymph nodes depends on the differentiation marker CD27 and ends after about 3 days; constant proliferation in tumor within the first 5 days.
- CFSE profile with undistinguishable generations can be analysed with the help of a mixture model utilizing the CFSE distribution of the undivided cells.
- Data suggests that antiCD40 treatment curbs influx into tumor but enhances proliferation.

Data-driven mathematical Model of Activation-Signal-Effects on T cell Kinetics

Quan-T-cell

Presenting Author: Jonas Mir

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Vaccination strategies to effectively induce long-term T cell memory via antigen-adjuvant formulations require profound knowledge about how acute responding T cells give rise to long-lived memory cells and how this mechanism is influenced by modulating factors. These mechanisms are however still poorly understood. Here we focus on how early antigen stimulus affects the resulting T cell response. To address this question in a quantitative manner, we utilize stochastic population dynamic modeling informed by in vivo single-cell fate mapping experiments. The model is chosen to be progressive, i.e. long-lived memory precursor T cells give rise to short-lived effector T cells. Our mathematical model describes these data accurately and, interestingly, predicts that the proliferation of the central memory precursor T cells is more dependent on antigen stimulus than the other T cell subsets, while cytokine stimulus selectively affects the effector compartment.

A mathematical framework to study ABO incompatible transplantation

SYSIMIT

Presenting Author: Sahamoddin Khailaie

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Antibodies against ABO blood group antigens cause rejection of kidney transplants by binding to donor vascular endothelium, leading to organ loss. Recipient desensitization can breach ABO barriers, and avoid antibody-mediated rejection of grafts. ABO incompatible (ABOi) kidney transplantation provides efficient use of organs regardless of ABO blood type. Despite excellent transplant outcomes, an understanding of the mechanisms that underlie acceptance of ABOi grafts is lacking. Further, thresholds of desensitization at which antibody-mediated damage can be predicted, or immunosuppressive burden can be reduced have not been defined. In order to study the mechanisms underlying the ABOi transplantation, we developed an ODE-based mechanistic mathematical model describing the interaction of immune components with the graft. The model considers immune interactions responsible for both T-cell- and antibody-mediated graft rejection. The constraints of building the model are the sufficient generality to capture the fundamental kinetics of the immune response, yet with sufficient complexity to adapt to patient- and graft-specific conditions and predict different outcomes. Our qualitative analysis of the model shows the importance of B cell number at the time of transplantation, such that a B cell depletion to a critical degree can avoid the peak of anti-graft immune response, and limit the response to a sub-critical but chronic phase. The model is aimed to be trained by immunological profiles obtained prior and during the recipient preconditioning process. These profiles include the amount of anti-A/B antibody titres, the degree of mismatch between recipient and donor, and immunological indices (cell counts, cytokines, etc.) of the recipient. By connecting recipient-specific immune indices to our mathematical model, we ultimately aim to assess the risk of graft rejection and stratify patients for individualized treatment.

Exploring the prognostic potential of characteristic inflammatory patterns in the breast tumor microenvironment

SYSIMIT

Presenting Author: Juan Carlos Lopez Alfonso

J. C. L. Alfonso (1), N. S. Schaadt (2), R. Schönmeyer (3), N. Krönke (2), G. Forestier (4), C. Wemmert (4), F. Feuerhake (2) and H. Hatzikirou (1)

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Although considerable progress has been made in understanding tumor-immune system interactions, little is known about the predictive value of inflammatory patterns paralleling tumor growth. The aim is to unravel the prognostic potential of the complex inflammatory tumor microenvironment (iTME) beyond the common concept of “tumor-infiltrating lymphocytes”, with particular focus on the triple-negative subtype of breast cancer (TNBC). We build on a previous physiologically calibrated model of interactions between immune and epithelial cells in non-neoplastic breast tissue undergoing fluctuating cell turnover during the menstrual cycle. Extension of the model allows for damaged epithelial cells to “undergo” oncogenic mutations (e.g. BRCA1/2) leading to cancer development. Taking advantage of the comprehensive evaluation of inflammatory patterns in breast tissues with and without neoplastic cell phenotypes will not only allow to better understand the role of inflammation in TNBC, but also to simulate different therapeutic scenarios to assess their success potential. The model will be fitted to spatial data extracted from whole slide images of female patients with TNBC, immunohistochemically stained for lymphocytes and macrophages. We combine a detection of regions of interest including tumor areas and normal lobules with an automatical identification of epithelial and immune cells. The spatial organization of individual cells is described by a graph-based approach. Together with an advanced iTME characterization, the model will help to elucidate the prognostic value of spatial distribution, functional orientation and composition of immune cells in breast cancer, with focus on the subset with the currently highest medical need for novel targeted therapies and high expected potential for immunomodulatory interventions. We are confident that our system medicine approach will lead to the definition of novel clinical decision-making criteria for breast cancer treatment.

A Biomathematical Model of Immune Response and Treatment in Mice with Pneumococcal Lung Infection

CAPSyS

Presenting Author: Sibylle Schirm

Sibylle Schirm1, Peter Ahnert1, Sandra Wienhold2, Sarah Berger2, Geraldine Nouailles-Kursar2, Norbert Suttorp2, Markus Loeffler1, Martin Witzenrath2, Markus Scholz1,3

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Pneumonia is considered to be one of the leading causes of death worldwide. The outcome depends on treatment and effectivity of the immune response of the host and cannot be predicted easily. For the treatment of pneumonia, new therapeutics such as D19 spiegelmer have been developed. These drugs are based on new mechanisms of action, so the therapeutic effects of these drugs supplementary to antibiotics are unclear. Hence, the modeling is important. Cytokin networks are complicated, and the modeling of all cytokines and chemokines would be too extensive, so we make a suggestion with this work. We construct a biomathematical model of the murine immune response during infection with pneumococcus aiming at predicting the outcome of treatment. The model consists on a number of non-linear ordinary differential equations describing the dynamics of the pneumococcal population, neutrophils, alveolar - and inflammatory macrophages, IL-6, MCP-1 and IL-10. The differentiation of peripheral blood monocytes into macrophages immigrating into BALF is included, and the destruction of the epithelial barrier allowing bacteria to pass through these defects into blood are now considered. The effects of antibiotic and barrier stabilizing drugs are modeled. Equations were derived by translating known biological mechanisms and assuming certain response kinetics. Unknown model parameters were determined by fitting the predictions of the model to time series data derived from mice experiments. Parameter fittings resulted in a good agreement of model and data for the experimental scenarios. The model can be used to predict the performance of alternative schedules of treatment. We conclude that we established a biomathematical model of pneumococcal lung infection in mice allowing predictions regarding the outcome of different treatment schedules. We aim at translating the model to the human situation in the near future.

BKV and CMV Coinfection in Renal Transplant Patients: Results from a Large Multicenter Study

e:Kid

Presenting Author: Arturo Blázquez Navarro

Arturo Blázquez Navarro, Chantip Dang-Heine, Michal Or-Guil, Chris Bauer, Ulrik Stervbo, Timm Westhoff, Christian Hugo, Petra Reinke, Birgit Sawitzki, Nina Babel

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BK virus (BKV), Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) reactivations are common after kidney transplantation (Tx), and associated with graft failure and increased morbidity and mortality. CMV is a risk factor for BKV and EBV reactivations, but the effects of viral coinfections remain unknown. Here we study the prevalence and clinical implications of the viruses in Tx. In a large prospective multicenter study, 3797 blood samples from 541 kidney transplant recipients were analyzed for BKV, EBV and CMV load by qPCR. The measurements were performed throughout eight visits during the first post-Tx year. Clinical characteristics, such as graft function (GFR) were collected in parallel. BKV was the most prevalent infection, had the higher viral load and the lowest clearing rates. Patients with BKV or CMV monoinfection over 10000 copies/mL had a significant renal function impairment 1-year post-Tx compared to non-infected. 115 patients were BKV CMV; both infections were significantly associated ($P<0.0001$). The temporal sequence of the two infections was not uniform: 52 patients showed BKV reactivation before CMV, 42 had CMV before BKV and in 21, both were detected simultaneously. Coinfected patients did not have higher viremias than monoinfected and did not show more rejection episodes. Nevertheless, coinfected patients showed a significant loss of renal function comparing to monoinfected infections. Even at lower thresholds (BKV > 1000 and CMV > 4000) than for monoinfected patients, coinfected patients showed a significant loss of GFR of 10.2 mL/min 1-year post-Tx ($P=0.03$). For EBV, a significant association ($P=0.02$) was found with CMV. High peak tacrolimus blood levels were significantly associated with viral reactivation. Our results demonstrate the effect of BKV and CMV coinfection for the long-term allograft function and highlight the importance of a good therapeutic monitoring and control of the viral reactivations, even at low viremia levels.

HLA class 1 SAB signatures provide a means to pre-kidney transplant high-accuracy risk assessment of acute T cell mediated rejection

e:Kid

Presenting Author: Harald Seitz & Michal Or-Guil

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Acute cellular rejection (ACR) is a major cause of chronic rejection and graft loss after kidney transplantation. Prevention of ACR is critical for the improvement of transplantation outcomes. In this study, we present a model for pre-transplant risk assessment of ACR based on solid phase HLA 1 single antigen bead (SAB) assay data. Thereby, 157 (sample/control: 77/80 patients) graft recipients were monitored for anti-HLA antibodies. Among the sub-group with detectable pre-transplant anti-HLA 1 antibodies, a characterization of the antibody profile was performed through SAB. The use of the machine learning method P-SVM allowed for the prediction of ACR based on SAB data, achieving a sensitivity of 76.5%, specificity of 88.9% and balanced accuracy 82.7%. The quality of the prediction is the highest among donor-independent risk assessment models. As the prediction is performed using quantitative non-thresholded SAB data, the model avoids the contested use of thresholds for the categorization of the results altogether. Taken together, our results show that both strong and weak binding interactions of antibodies and HLA 1 antigens hold information of high value for the risk assessment of ACR. This is the first model that is able to predict ACR pre-transplantation in the literature.

Asymmetric Link detection via a generalized ESABO approach

SysINFLAME

Presenting Author: Jens Christian Claussen

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Jacobs University Bremen

Mutualisms in biological populations are widespread from bacteria to mammals. Mutualistic interactions can be positive (synergistic) or negative. Often even in microbial data the number of available samples is marginally sufficient to allow for detection of interactions, especially for the low-abundance species that may carry important information in clinical context. The recently introduced ESABO method (PloS Comp Biol 13: e1005361 (2017)) utilizes an information-theoretic approach to evaluate binarized abundances and was demonstrated to detect interaction links that were not apparent in the classical correlation analyses. ESABO provides high (resp. low) scores if joint occurence is higher (resp. lower that in surrogate data. As so far, ESABO concludes on negative interactions when co-occurrence is lower than expected. However, this can be due to asymmetric (unidirectional parasitic) interaction in any of two directions, or due to symmetric interactions. Here we generalize the ESABO method to analyze co-abundance data resolving for asymmetry between the interactions.

Integration of cellular signalling cascade into whole-body and pharmacokinetic model: Estimating cellular responses to administered Interferon Alpha doses in humans.

Presenting Author: Priyata Kalra

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Administration of the cytokine interferon alpha (IFN-α) is a standard therapy against chronic hepatitis C infection- the leading cause of liver diseases. However, the IFN-α signalling pathway remains enigmatic due to its specificity of antiviral responses and differences of its efficacy in- vitro vs in-vivo. Moreover, the success of the treatment is patient dependent. A mechanistic assessment of the underlying physiological processes across different scales of biological organization is hence necessary to optimize IFN-α treatment design. Pharmacokinetics model combined with systems biology model would allow us to exploit the cellular response at the target site. This will result in more realistic mechanism based pharmacokinetic/dynamic model opening exploration in a wide spectrum of applications in current drug design, eg. Ranking of the biomarker candidate or sub-population analysis. Using the case of IFN-α treatment in humans we present here a novel approach for the integration of detailed molecular pathway models at the cellular level into physiology-based pharmacokinetic (PBPK) models at the organism scale. The multiscale model describes the whole-body distribution of IFN-α and the resulting cellular signalling response in the JAK/STAT pathway in the liver. The model sheds light on the changes in signalling behaviour at the target site when considered in an in-vivo context capturing the non-linear pharmacokinetic behaviour of IFN-α within the body. The presented model is a significant step towards a mechanistic assessment of the mutual dependencies of drug pharmacokinetics governing tissue specific availability of a therapeutic agent and the resulting therapeutic response at the molecular-response scale with clearer resolution.

Simulation of omics data for machine learning

ComorbSysMed

Presenting Author: Stephan Seifert

Stephan Seifert, Silke Szymczak

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Methods of machine learning are promising approaches for the analysis of complex omics data sets that are obtained in biomedical research and that feature complex correlation structures. In order to compare different methods and to characterize particular properties of machine learning tools the investigation of simulated omics data sets is essential. For the simulation of high-dimensional omics data with complex correlation structures, simulation frameworks and packages have been developed that can be exploited to obtain suitable data relatively fast and easily. We will introduce some of these frameworks including an R package for weighted correlation network analysis (WGCNA)1, the ultimate microarray prediction and inference and reality engine (Umpire)2 and a Java tool called Synthetic Transcriptional Regulatory Networks (SynTRen)3. The different implementations, as well as pros and cons of the respective approaches will be discussed. References: [1] Langfelder, P., and Horvath, S. (2008). WGCNA: an R package for weighted correlation network analysis. BMC Bioinformatics 9, 559. [2] Zhang, J., Roebuck, P.L., and Coombes, K.R. (2012). Simulating gene expression data to estimate sample size for class and biomarker discovery. Int J Advances Life Sci 4, 44–51. [3] Van den Bulcke, T., Van Leemput, K., Naudts, B., van Remortel, P., Ma, H., Verschoren, A., De Moor, B., and Marchal, K. (2006). SynTReN: a generator of synthetic gene expression data for design and analysis of structure learning algorithms. BMC Bioinformatics 7, 43.

Evaluation of variable selection methods for random forests and omics data sets

ComorbSysMed

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Machine learning methods such as random forests are promising approaches for prediction based on high dimensional omics data sets. They provide variable importance measures to rank predictors according to their predictive power. If building a prediction model is the main goal of a study, often a minimal set of variables with good prediction performance is selected. However, if the objective is the identification of involved variables to find active networks and pathways, approaches that aim to select all relevant variables should be preferred. We evaluated several variable selection procedures based on simulated data as well as publicly available experimental methylation and gene expression data. Our comparison included the Boruta algorithm, the Vita method, recurrent relative variable importance (r2VIM), a permutation approach (Perm) and its parametric variant (Altmann) as well as recursive feature elimination (RFE). In the simulation studies, Boruta was the most powerful approach, followed closely by the vita method. Both approaches demonstrated similar stability in variable selection, although vita was the most robust approach under a pure null model without any predictor variables related to the outcome. In the analysis of the different experimental data sets vita demonstrated slightly better stability in variable selection and was less computationally intensive than Boruta. In conclusion, we recommend the Boruta and the Vita approaches for the analysis of high dimensional data sets. Vita is considerably faster than Boruta and thus more suitable for large data sets, but only Boruta can also be applied in low dimensional settings.

Systems medicine approach for prediction of hemodynamic outcome after aortic valve replacement

SMART

Presenting Author: Sarah Nordmeyer

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Complex flow profiles in the ascending aorta in patients with aortic valve stenosis (AS) have been associated with energy loss and progression in aortic dilation, which affects morbidity and mortality of patients. Virtual valve replacement modeling is part of the whole organ model within the SMART project (e:Med Systems Medicine, BMBF) aiming to help in the decision making process of choosing the surgical treatment with optimal post-treatment hemodynamic outcome using a systems medicine approach. In patients with AS cardiac MRI before and after surgical aortic valve replacement (AVR) was used to collect patient specific anatomic and hemodynamic data. Computational Fluid Dynamics was performed for virtual valve replacement testing different possible treatment options for prediction of postoperative hemodynamic outcome. Myocardial energy expenditure and its postoperative change were calculated using imaging and clinically acquired data. Different surgical treatment strategies (mechanical and biological valves for example) lead to significant differences in hemodynamic outcome with regard to blood flow profiles and left ventricular work efficiency. Virtual treatment allows prediction of outcome scenarios of different therapeutical options with the aim to optimize treatment outcome. A systems medicine approach for predicting postoperative hemodynamic outcome helps to establish individualized strategies for treatment decision making in surgical AVR.

Establishment of Multi-OMICs Pathway Analysis in Human Atrial Fibrillation

symAtrial

Presenting Author: Ines Assum

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The use of different OMIC technologies enables the investigation of different molecular levels in health and disease. However, the integration of several layers of OMICs data is still challenging and requires specifically designed methods. Here, we present a multi-OMICs approach to understand the pathophysiology of Atrial Fibrillation (AF). As a part of the consortium Systems Medicine of Atrial Fibrillation (symAtrial), our aim is to infer molecular mechanisms of AF at the level of distinct pathways representing biological processes deregulated in disease. Using state-of-the-art technologies, transcriptomics and proteomics were measured in atrial appendage tissue samples of 135 patients undergoing heart surgery. We performed differential analysis of gene expression and protein concentration between AF (n=32) and non-AF patients (n=64) considering various models with multiple AF subtypes and clinically relevant covariates. We calculated, evaluated and compared existing methods for pathway enrichment for their potential to integrate multiple OMICs: Gene Set Enrichment Analysis (GSEA) on ranked lists takes into account the direction of the effect. However, applying GSEA is restricted to a single data type. Therefore, results need to be combined in an ad-hoc manner. Multilevel ONtology Analysis (MONA), a Bayesian approach, directly addresses this challenge and allows for simultaneous analysis of multiple data types. We also studied extensions of MONA including direction of effect and more than two layers of information. To compare methods, we tested all models with simulated data using positive and negative controls over a spectrum of various false positive and false negative rates. Keeping simulations as close as possible to our real data allowed us to estimate effect sizes and detection accuracy necessary for successful identification of regulated pathways. Based on the results, we selected the most suitable approach for our data to identify pathways altered in AF.

A Mendelian Randomization study of NT-proBNP and Atrial Fibrillation

symAtrial

Presenting Author: Markus O. Scheinhardt (1)

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Atrial Fibrillation (AF) is a common cardiac arrhythmia, which can lead to serious complications such as stroke or heart failure. The N-terminal pro B-type natriuretic peptide (NT-proBNP) has been shown to be a biomarker for AF, but its causality remains unclear. In this study, our research group (symAtrial) uses a modern approach of Mendelian Randomization to infer causality between NT-proBNP and AF. A single-sample MR was conducted using individual level data on 4197 controls and 133 prevalent AF cases with a European background from the Gutenberg Health Study (GHS) cohort. The genetic instrument uses significantly associated SNPs from the genome wide association study (GWAS) in the same dataset. The genetic instrument showed a high F-statistic and no association with any of the known confounders in the association of NT-proBNP and AF. The ratio method with an unweighted genetic risk score was used to evaluate causality. We further verified our results using the two stage least square (2SLS) method. Both methods demonstrated a significant causal association between NT-proBNP and AF. Our study provides new insights into the underlying biology of AF. Replication in independent samples is required.

Loss of zebrafish Smyd1a interferes with myofibrillar integrity without triggering the misfolded myosin response

SYMBOL-HF

Presenting Author: Christoph Paone

Christoph Paone, Steven Rudeck, Wolfgang Rottbauer, Steffen Just

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Sarcomeric protein turnover needs to be tightly balanced to assure proper assembly and renewal of sarcomeric units within muscle tissues. The mechanisms regulating these fundamental processes are only poorly understood, but of great clinical importance since many cardiac and skeletal muscle diseases are associated with defective sarcomeric organization. The SET- and MYND domain containing protein 1b (Smyd1b) is known to play a crucial role in myofibrillogenesis by functionally interacting with the muscle myosin chaperones Unc45b and Hsp90α1. In zebrafish, Smyd1b, Unc45b and Hsp90α1 are part of the misfolded myosin response (MMR), a regulatory transcriptional response that is activated by disturbed myosin homeostasis. Genome duplication in zebrafish led to a second paralogous smyd1 gene, termed smyd1a. Morpholino- and CRISPR/Cas9-mediated knockdown of smyd1a led to significant perturbations in sarcomere structure resulting in decreased cardiac contractility as well as skeletal muscle function. Similar to Smyd1b, we found Smyd1a to specifically localize to the sarcomeric M-band in fast-twitch muscle fibers and cardiac muscle tissue. Ectopic overexpression of smyd1a efficiently compensated for the loss of Smyd1b in flatline (fla) mutant zebrafish embryos and rescued the myopathic phenotype as well as suppressed the MMR in Smyd1b-deficient embryos, suggesting overlapping functions of both Smyd1 paralogs. Interestingly, Smyd1a is not transcriptionally activated in Smyd1b-deficient fla mutants, demonstrating lack of genetic compensation despite the functional redundancy of both zebrafish Smyd1 paralogs.

Role of HDAC1 in cardiomyocyte proliferation during heart development

SYMBOL-HF

Presenting Author: Anja Bühler

Sofia Hirth, Steffen Just, Wolfgang Rottbauer

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Following myocardial infarction, mammalian cardiomyocytes (CM) lack the ability to proliferate and replace the damaged cardiac tissue, eventually leading to heart failure and death. In contrast, CMs in adult zebrafish can re-enter the cell cycle and regenerate damaged cardiac muscle tissue completely. We hypothesize that by studying the mechanisms that regulate CM proliferation in development we may elucidate new candidate genes that may also be involved in heart regeneration. Hence, we characterized the zebrafish mutant baldrian (bal) which displays a cardiac growth defect. In mutants early heart development proceeds normally until 48 hours post fertilization (hpf). Following 48 hpf bal hearts have a strikingly small ventricle and monolayered myocardium. The number of progenitors and the rate of CM apoptosis were not altered in these mutants. However, CM counts demonstrated a significant decrease in ventricular CM number at 72 hpf in bal embryos. EdU incorporation assays showed fewer cycling CMs, indicating that cell cycle defects might be the cause for the ventricular hypoplasia in bal mutants. To identify the mutation underlying this phenotype, baldrian was positionally cloned, revealing a missense mutation in the histone deacetylase 1 (hdac1) gene, leading to a strong decrease of HDAC1 on protein level. Treatment of cultured primary neonatal rat CMs with HDAC1 inhibitor significantly decreased the number of proliferating rat CMs in vitro, without triggering apoptosis. These findings suggest a conserved role of HDAC1 in CM proliferation in vertebrates. Our future goals aim at understanding the molecular mechanisms by which HDAC1 regulates cell cycle progression in embryonic CMs.

A semantic characterization of the landscape of heart failure zebrafish models

SYMBOL-HF

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The molecular etiology of human heart failure is poorly characterized due to the limited access to cardiac tissue.

Genetic model organisms like, mice and zebrafish can facilitate the understanding of the genetic background of this disease. The identification of molecular markers and pathways is mandatory in the detection of possible disease causes at the molecular level.

In this work, we provide a comparative analysis of RNA sequencing data (31953 features) from a cohort of 180 zebrafish (in total 90 mutants vs 90 controls) comprising 6 different heart failure phenotypes (bradycardia/arrhythmia, heart development, heart valve defect, hypoplasia myofibrillogenesis defects, weak contractility). In 10x10 cross-validation experiments, we achieved accuracies of 87.3% or higher in discriminating these phenotypes.

Our experiments are based on a semantic multi-classifier system that incorporates existing domain knowledge in the training process of a classification model. We utilize interpretable marker combinations that reflect higher level processes such as signalling pathways, e.g. “Wnt-signalling“. The KEGG database and the Gene Ontology are utilized as external knowledge base. Each marker subset is then used for a specialized training of a corresponding domain expert (or base classifier). A mixture of the best experts will provide the final prediction. The most prominently selected processes were "Fatty acid elongation", "Butanoate metabolism", "Biosynthesis of unsaturated fatty acids". The gene sets and also individual genes associated to these pathways are currently being investigated by additional wet lab experiments.

Multi-Scale Modelling of Excitation Contraction Coupling in Ventricular Cardiomyocytes

Presenting Author: Wilhelm Neubert

Wilhelm Neubert(1), Chamakuri Nagaiah(2), Janine Vierheller(1), Stephen Gilbert(1), Martin Falcke(1)

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Calcium induced Calcium Release (CICR) is a central mechanism on the pathway from electrical signal to contraction of a cardiomyocyte. It involves a wide range of spatial scales, from the nanometer wide diadic cleft spaces between junctions of the Sarcoplasmic Reticulum (SR) and the plasma membrane to cell wide depolarization, as well as a wide range of timescales from sub-millisecond channel state transitions to dynamics that emerge only over the course of many heartbeats. We present here a model that encompasses all spatial and temporal scales of Calcium signaling in the left ventricular cardiomyocyte and their interconnections in high detail and precision.·Cell wide reaction-diffusion equations describe the intracellular concentration fields of Calcium and its buffers in the cytosol and SR. The source terms of these PDEs are (partially) generated by highly stochastic, very localized, and strong Calcium currents that originate in the diadic clefts. The clefts contain representations of individual channels as discrete, continuous time Markov chains, coupled by strong local gradients inside the diadic space.·Individual cleft spaces are coupled by both the diffusion equations in the cytosol and SR as well as the cell wide membrane potential, which is modelled by a set of·ordinary differential equations (ODEs). The Monte-Carlo simulations of the channel dynamics lead to a high frequency of significant changes in the PDEs, which would limit the Finite Element PDE solver's time step size too drastically to be practical. We apply a novel time step management combined with linear estimates of the PDE solution on very short time scales to lift this restriction and render simulations efficient.

Meta-analysis using sparse Bayesian multiple logistic regression improves power of GWAS

e:AtheroSysmed

Presenting Author: Saikat Banerjee

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Genetic variants in genome-wide association studies (GWAS) are tested for disease association mostly using simple regression, one variant at a time. Multiple regression can improve power by aggregating evidence from multiple nearby variants. It can also distinguish disease-coupled variants from those which are merely correlated with a coupled variant. However, it requires individual genotype data, limiting its applicability when combining several GWAS. Moreover, multiple logistic regression to model binary phenotypes in case-control GWAS requires inefficient sampling schemes to integrate over the variant effect sizes. Our sparse Bayesian multiple LOgistic REgression (B-LORE) method overcomes these two drawbacks. We propose a quasi-Laplace approximation to analytically integrate over variant effect sizes. The resulting marginal likelihood functions of individual GWAS are approximated by multivariate normal distributions. Their means and covariance matrices serve as summary statistics for combining several GWAS. Additionally, B-LORE can integrate functional genomics tracks as priors for each variant's causality. To test our method, we simulated synthetic phenotypes for real genotypes. B-LORE improved the prediction of loci harboring causal variants and the variant fine mapping. We also used B-LORE for a metanalysis of five small GWAS for coronary artery disease (CAD). We pre-selected the top 50 loci with SNPTEST / META, which included 11 loci discovered by a 14-fold larger meta-analysis (CARDIoGRAMplusC4D). While single-SNP tests discovered only 3 of them with genome-wide significance, B-LORE discovered all of them with causal probability >95%. Of the 12 other loci discovered by B-LORE, 3 are known from other CAD GWAS and 6 are associated with well-known CAD risk-related blood metabolic phenotypes. B-LORE also prioritized the SNPs instead of predicting similar p-values for all correlated SNPs.

Software availability: https://github.com/soedinglab/b-lore.

Posters

The added value of non-linear analysis in systems medicine analyses

e:AtheroSysmed, IntegraMent

Presenting Author: Bertram Müller-Myhsok

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Correlation or (more generally) dependence can indicate a statistical association between random variables, which is an essential metric in data analysis. In biology, the methods for linear associations are often favored for the low computational complexity and the easy interpretation of result. On the other hand, it neglects the fact that non-linear associations widely exist in complex biological system. Based on gene-expression data as an example system and the Randomized Dependence Coefficient (RDC) as an exemplary metric we investigate the amount of non-linearity in biological systems, being able to demonstrate considerable amounts of nonlinearity being present. Furthermore, we are able to show that using such information in analytic procedures, such as unsupervised learning, significant gains in performance are achievable.

Cross-disorder risk gene CACNA1C differentially modulates susceptibility to psychiatric disorders during development and adulthood

IntegraMent

Presenting Author: Jan M. Deussing

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Single nucleotide polymorphisms (SNPs) in CACNA1C, the α1C subunit of the voltage-gated L-type calcium channel Cav1.2, rank amongst the most consistent and replicable genetics findings in psychiatry, and have been associated with schizophrenia, bipolar disorder and major depression. However, genetic variants of complex diseases often only confer a marginal increase in disease risk, which is additionally influenced by the environment. Here we show that embryonic deletion of Cacna1c in forebrain glutamatergic neurons promotes the manifestation of endophenotypes related to psychiatric disorders including cognitive decline, reduced sociability, hyperactivity and increased anxiety. Additional analyses revealed that depletion of Cacna1c during embryonic development also increases the susceptibility to chronic stress, which suggest that Cav1.2 interacts with the environment to shape disease vulnerability. Remarkably, this was not observed when Cacna1c was deleted in glutamatergic neurons during adulthood, where the later deletion even improved cognitive flexibility, strengthened synaptic plasticity and induced stress resilience. In a parallel gene × environment design in humans, we additionally demonstrate that SNPs in CACNA1C significantly interact with adverse life events to alter the risk to develop symptoms of psychiatric disorders. Our results suggest a differential role for Cav1.2 during development and adulthood in shaping the risk for developmental and stress-related psychopathologies, and may direct future efforts towards more effective treatment strategies.

Probing loss-of-function of the neuropsychiatric risk factor RB1CC1 in human neural cells

IntegraMent

Presenting Author: Kristina Rehbach

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Experimental studies on molecular mechanisms of neuropsychiatric diseases have been largely restricted to animal models or immortalized cell lines due to limited access to human brain tissue. However, these reductionist models for selected genetic mutations cannot reflect human, brain-specific, genetic and cellular alterations underlying pathogenesis. With novel genome-editing technologies it is now possible to overcome these serious restrictions via inserting disease-associated mutations into human iPSCs and subsequent differentiation into neurons and glia. This approach yields isogenic pairs of mutated and control cells allowing to precisely delineate the functional impact of gene variants due to the elimination of confounding genetic background variants. We set out to understand the role the risk factor RB1CC1, a tumor suppressor gene, implicated in the regulation of cell proliferation, differentiation and migration as well as cell survival and autophagy. Rare RB1CC1 affecting duplications are associated with schizophrenia and intellectual disability (Degenhardt et al., 2013). Furthermore, de novo loss-of-function mutations are known in two independent patients with schizophrenia (Xu et al., 2012, unpublished). To explore the impact of reduced gene dosage of RB1CC1, we generated a frame shift mutation in one or both alleles of the gene using CRISPR-Cas9 nickase. Edited iPSC clones were quality-controlled by genotyping PCR as well as SNP karyotyping, and loss of RB1CC1 protein was confirmed by immunoblotting. We differentiated several iPSC clones with two, one or no functional alleles into cortical progenitors and neurons. These cultures are used to assess potential phenotypic differences. Exploiting the expertise of the IntegraMent consortium, we aim at transcriptomic and proteomic profiling of RB1CC1 mutant and control neurons to decipher pathways dysregulated by mutant RB1CC1, contributing to neural dysfunction and the pathogenesis of neuropsychiatric disease.

A model-based approach for relating neural activity to behaviour with an application to extinction learning in operant alcohol self-administration

IntegraMent, SysMedAlcoholism

Presenting Author: Hazem Toutounji

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Neural activity from higher cortical areas in awake, behaving animals has highly heterogeneous population-wide response properties. Relating this high-dimensional and dynamic neural activity to behavioural covariates remains challenging. Here we tackle this issue by developing a class of behavioural and neural change models. After estimating the parameters of these models from data, behaviour may be matched to its neural correlates by relating the inferred behavioural parameters to their neural counterparts. The behavioural model assumes a nonhomogeneous Bernoulli process that represents the probability in time that a specific behavioural response occurred. The neural model assumes a nonhomogeneous Poisson process, representing the expected number of spikes emitted by a neuron in time. Both the behavioural and neural processes are modelled by the sum of a baseline value and several sigmoidal functions, each of which corresponding to a single change event in the statistics of the process. Each sigmoid is parametrised by the time it reaches 50% of its maximum value (i.e., the change point), the time scale of the change and the magnitude or weight of change. These model parameters are estimated from data by maximum likelihood. Specifying the number of change events that significantly contribute to explaining the activity of a neuron or the behavioural response probability is achieved using likelihood ratio test statistics. Here, application of this methodology is demonstrated by fitting behavioural and neural models to rat medial prefrontal cortex (mPFC) recordings during the extinction of operant alcohol self-administration behaviour. Interestingly, the neural change models show that neural events are concentrated around the behavioural change points as identified by the behavioural model. This indicates that the activity of mPFC neurons are in temporal agreement with the behavioural processes that drive extinction learning during operant alcohol self-administration.

Assessing computational dynamics from fMRI time series using recurrent neural networks

IntegraMent, SysMedAlcoholism

Presenting Author: Georgia Koppe

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Cognitive functions arise through the coordinated activity between many interconnected brain regions and are thought to be implemented in terms of the stochastic and dynamical properties of the underlying network. For example, non-linearly connected networks foster a multitude of stochastic dynamical phenomena such as multi-stability, complex limit cycles and attractor-hopping, which implement cognitive computations related to memory and decision making. By adjusting their internal connections, neural networks may further change their dynamical properties over time, enabling adaptive behavior. Inferring stochastic network dynamics from neural time series may therefore advance our understanding of neuro-cognitive mechanisms and allow for deeper insights into psychiatric disorders. From this perspective, psychiatric symptoms and cognitive dysfunction are rooted in changes of the underlying dynamical system properties and the inability to successfully adapt these properties in a given context. One prominent approach to the reconstruction of stochastic network dynamics from experimental recordings is the use of state space models (SSMs). SSMs treat the often high-dimensional noisy recordings as being generated by an underlying (usually much lower dimensional) latent dynamical system subject to process noise. In this way, they yield essential and compact information about the underlying system's trajectories as well as its governing dynamics. However, so far only few of the proposed models capture non-linear dynamics essential to emulate many crucial phenomena related to cognition, and hardly any capture non-stationary processes key to learning and adaptive behavior. Building on a previous model developed in our group (Durstewitz, 2017), here we develop an SSM based on a recurrent neural network model with non-stationary latent process designed to assess dynamics from functional magnetic resonance imaging recordings and thus directly applicable to psychiatric data sets.

A hierarchical stochastic model for bistable perception

PsychoSys

Presenting Author: Stefan Albert

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Viewing of ambiguous stimuli can lead to bistable perception alternating between the possible percepts. During continuous presentation of ambiguous stimuli, percept changes occur as single events, whereas during intermittent presentation of ambiguous stimuli, percept changes occur at more or less regular intervals either as single events or bursts. Response patterns can be highly variable and have been reported to show systematic differences between patients with schizophrenia and healthy controls. Existing models of bistable perception often use detailed assumptions and large parameter sets which make parameter estimation challenging. Here we propose a parsimonious stochastic model that provides a link between empirical data analysis of the observed response patterns and detailed models of underlying neuronal processes. Firstly, we use a Hidden Markov Model (HMM) for the times between percept changes, which assumes one single state in continuous presentation and a stable and an unstable state in intermittent presentation. The HMM captures the observed differences between patients and healthy controls, but remains descriptive. Therefore, we secondly propose a hierarchical Brownian model (HBM), which produces similar response patterns but also provides a relation to potential underlying mechanisms. The main idea is that neuronal activity is described as an activity difference between two competing neuronal populations reflected in Brownian motions. This differential activity generates switching between the two percepts and between stable and unstable states with similar mechanisms on different neuronal levels. With a small number of parameters, the HBM can be fitted closely to a high variety of response patterns and captures group differences between healthy controls and patients with schizophrenia. At the same time, it provides a link to mechanistic models of bistable perception, linking the group differences to potential underlying mechanisms.

Metformin reverses TRAP1 mutation- associated alterations in mitochondrial function in Parkinson's disease

Mito-PD

Presenting Author: Julia C Fitzgerald

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Parkinson's disease is an aetiologically heterogeneous syndrome caused by a combination of genetic and environmental risk factors. The advancement of genetic testing and identification of patient endophenotypes has given hope for the emerging field of individualized medicine. Mitochondrial dysfunction, ensuing cellular energy failure and oxidative stress may be one important disease pathway in a subgroup of Parkinson's disease patients. The aim is that these patients can be therapeutically targeted. The mitochondrial proteins TRAP1 and HTRA2 are phosphorylated downstream of PD protein PINK1 but the downstream signaling is unknown. In our human cell models, TRAP1 overexpression is protective, rescuing HTRA2 and PINK1-associated mitochondrial dysfunction and suggesting that TRAP1 acts downstream of HTRA2 and PINK1. HTRA2 regulates TRAP1 protein levels, but TRAP1 is not a direct target of HTRA2 protease activity. Following genetic screening of Parkinson's disease patients and healthy controls, we also report the first TRAP1 mutation leading to complete loss of functional protein in a patient with late onset Parkinson's disease. Analysis of fibroblasts derived from the patient reveal that oxygen consumption, ATP output and reactive oxygen species are increased compared to healthy individuals. This is coupled with an increased pool of free NADH, increased mitochondrial biogenesis and loss of mitochondrial membrane potential. These data highlight the role of TRAP1 in the regulation of energy metabolism. The diabetes drug metformin reverses mutation-associated alterations and restores mitochondrial membrane potential. Our data show that TRAP1 acts downstream of PINK1 and HTRA2 for mitochondrial fine tuning, whereas TRAP1 loss of function leads to reduced control of energy metabolism. We are now performing pilot studies for mitochondrial biomarkers in blood cells with the hope of stratifying Parkinson's disease patients for better targeted therapies.

Genome-edited, TH-expressing neuroblastoma cells as a disease model for dopamine-related disorders: a proof-of-concept study on DJ-1-deficient parkinsonism

Mito-PD

Presenting Author: Jannik Prasuhn

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Impairment of the dopaminergic (DA) system is a common cause of several movement disorders including Parkinson's disease (PD). However, little is known about the underlying disease mechanisms, mostly due to lack of cellular models efficiently producing dopamine. The recent development of stem-cell-based protocols for the generation of DA neurons partially solved this issue, however, this technology is costly and time-consuming. Other commonly used cell lines, i.e. neuroblastoma (SHSY5Y) and PC12 cells, either do not express DA at all or require additional, only partially efficient differentiations in order to produce DA. Here we showed that transgenic SH-SY5Y cells, ectopically expressing tyrosine hydroxylase (SHTH+), can be used as a homogenous, DA-producing model to study alterations in DA metabolism. We demonstrated that SHTH+ produce high levels of DA, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) making this model suitable to investigate not only alterations in DA synthesis but also its turnover. We also provide evidence for the presence of other enzymes involved in DA synthesis and its turnover in these cells. Finally, we showed that these cells can easily be genetically modified using CRISPR/Cas9 technology in order to study genetically defined forms of movement disorders using DJ-1-linked PD as a model.

A theory driven in-vitro approach to understand collective neuronal dynamics in neurodegenerative diseases

Presenting Author: Jonas Franz

Jonas Franz, Manuel Schottdorf, Alexander Schmidt, Fred Wolf

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A major problem in the research of neurodegenerative diseases is the missing link between in-vitro data and observed clinical symptoms. Especially, the amyloid hypothesis in Alzheimer's disease (AD), mainly driven by molecular analysis of early-onset genetic dementia, failed so far to result in an effective treatment [1]. The discrepancy between molecular hypothesis and clinical outcome may also be caused by the fact that single cell electrophysiological recordings do not capture ongoing complex network dynamics in neurodegenerative diseases like AD. The in-vitro tool introduced here aims to understand the neuronal system from a different perspective. A multi-electrode array (MEA) embedded in a holographic setup allows to control and record neuronal activity at the same time. This is achieved by optogenetics, specifically the expression of the algal ion channel ChR2 using a viral vector, introducing an effective, optically tunable drive. MEA-recordings in homogeneously and heterogeneously driven setups allow to test predictions made by a novel approach to a mean field theory of a balanced state network. This analytical approach provides firing rate distributions from a small set of network parameters only. It shows promising results in qualitatively explaining experimentally observed changes in firing rate distributions under the introduction of heterogeneity to the network. For example the increased occurrence of both silent and hyperactive neurons in mice models of AD can be observed [2]. The theoretical approach combined with the in-vitro, optogenetic tool might help to shed light on collective dynamics of neurons under physiological and pathological conditions. [1] Holmes, C. et al. (2008). Lancet, 372, 216–223. [2] Busche, M. A., & Konnerth, A. (2015). BioEssays, 37(6), 624–632.

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SYSTEMS MEDICINE

Poster Presentations

Systems Medicine Approaches in Clinics

Combination of multiparametric PET/MRI Imaging and NMR Metabolomics as a potential non-invasive method to predict therapeutic outcome in HCC

Multiscale HCC

Presenting Author: Patricia Wenk

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Hepatocellular carcinoma (HCC) is the second most common cause of cancer deaths worldwide. Sorafenib (Sib) is currently the only approved systemic treatment of advanced HCC, with only a modest improvement in overall survival due to development of secondary therapy resistance. Thus, we aimed to investigate available biomarker and imaging procedures to identify resistance mechanisms and predict therapy response. In our translational approach, combined PET/MRI using 18F-FDG (glucose metabolism) and 11C/18F-Choline (membrane synthesis) prior and during treatment with Sib was used in both HCC Patient as well as mice with orthotopically induced HCC, driven by either c-Myc/Akt-1 (CaMIA; Sib resistant) or c-Myc/NRasG12V (CaMIN; secondary resistance to Sib). Additionally, NMR metabolomics of patient derived samples from plasma, urine as well as murine tumor biopsies were analyzed. Both murine tumor types showed differences in 18FDG uptake pattern in overall liver tissue. Before developing secondary resistance CaMIN mice showed a significantly lowered 18FDG uptake compared to CaMIA mice. Choline-PET revealed a decreased uptake for all CaMIN mice in correlation to tumor development. However, HCC-patients with progress under Sib therapy presented a trend to higher 18FDG uptake, while the results of Choline-PET were inconsistent. Metabolomics of CaMIN-driven murine tumors showed a significant increase of HDL and LDL-specific NMR signals and upregulation of diverse metabolites involved in glycolysis due to upcoming resistance. NMR analysis of lipoproteins in patient plasma indicated a correlation of LDL and HDL particle size with treatment response. Also, PC analysis of metabolites in patients' urine yielded similar findings. New diagnostic approaches are needed in personalized medicine to predict secondary resistance development. Combining multiparametric imaging and metabolomics is a promising tool to asses metabolic reprogramming of HCC leading to Sib resistance.

Multiscale analysis by acquisition of image and molecular fingerprints for patients under systemic treatment of hepatocellular carcinoma

Multiscale HCC

Presenting Author: Franz Hilke, Marius Horger and Michael Bitzer

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Hepatocellular carcinoma (HCC) is among the five leading cancer entities worldwide and the multi-tyrosine kinase inhibitor Sorafenib has been the only approved drug during the last ten years. So far no reliable biomarker is able to prospectively predict treatment outcome. In this project we acquire comprehensive image and molecular fingerprint data to identify mechanisms that determine the outcome to guide individual treatment decisions. We present a comprehensive data analysis for a patient who developed a complete remission upon treatment with Sorafenib. Multimodality imaging diagnostic (Perfusion-CT, MRI, 18F-FDG- and 11Choline-PET), fresh frozen and liquid biopsies were performed at baseline and week 4. All samples were characterized by whole exome sequencing, liquid biopsies were analyzed using mFAST-SeqS. Metabolic parameters were determined in blood and urine samples by NMR spectroscopy. The patient presented with multifocal involvement of the liver by highly arterialized HCCs. Under treatment, MRI T1w and T2w signals increased, accompanied by a drop in tumor perfusion. Choline and FDG uptake remained stable at week 4, whereas tumor vascularization continuously decreased and necrotic parts enlarged. During at least 14 months, the liver did not show any residual tumor perfusion. We identified 108 single nucleotide alterations at baseline and 121 at week 4 with a decrease in plasma ctDNA content during treatment. Metabolomic analysis identified a unique pattern, with deviating quantifications compared to other patients. Interestingly, despite tumor control in the liver, a suprarenal metastasis developed after more than one year of continued treatment. Comprehensive data of image and molecular fingerprints from this patient will be presented. Furthermore we will provide additional genetic data from a suprarenal metastasis that developed despite continued treatment. We expect to identify highly relevant parameters to guide individual treatment decisions in HCC.

Finding deregulated subnetworks with multi-omic clinical data

Multiscale HCC

Presenting Author: Sebastian Winkler

Sebastian Winkler, Matthew Divine, Oliver Kohlbacher

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Mining clinical multi-omics data for possible meaning and interpretation is decisive in the process of bringing systems medicine approaches to the clinics. Here, we are concerned with the interpretation of omics-data with respect to directed network representations of biology and its application to data from hepatocellular carcinoma patients. We developed a method which can help in finding deregulated subnetworks within a bigger regulatory network where “deregulated” is defined in terms of the multi-omics data. Our method is also suitable for flexibly incorporating additional semantics concerning the nodes of the network by being able to find subnetworks which are rooted in particular types of nodes (representing membrane receptors for example) and end in nodes of other types (for example representing transcription factors of interest). Compared to more classical methods for functional interpretation, like gene set enrichment, our method exhibits the advantages of not relying on predefined pathway concepts and directly leveraging the topology of the regulatory or signaling network which enables for example the detection of cross talks between classical predefined pathways. We applied our method to genomic, transcriptomic and methylomic data of hepatocellular carcinoma patients from the Multiscale HCC project. We found patients-specific deregulated subnetworks capturing different aspects of the data, for example how the omics-data of each patient relates to well-known Sorafenib targets within a subnetwork context. Comparing the subnetworks found for the Multiscale HCC patients to subnetworks we found based on The Cancer Genome Atlas (TCGA) HCC data provided further means of contextualizing the subnetworks of the patients. An implementation of the method which is based on a combination of techniques from combinatorial optimization and graph algorithms is available at https://github.com/sebwink/deregnet under the MPL2 license.

Epigenetic regulation of the tryptophan-degrading enzyme indoleamine-2, 3-dioxygenase in human breast cancer

GlioPath

Presenting Author: Christiane Opitz

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Kynurenine formation by the tryptophan-catabolic enzyme indoleamine-2,3-dioxygenase (IDO1) promotes tumor immune evasion and pharmacological inhibition of IDO1 suppresses tumor growth in preclinical models of breast cancer. As immune checkpoint inhibitors may be of limited efficacy in breast cancer, a better understanding of the expression of additional targetable immunomodulatory pathways is of importance. We therefore investigated the regulation of IDO1 expression in different breast cancer subtypes. We identified estrogen receptor alpha (ER) as a negative regulator of IDO1 expression. Serum kynurenine levels as well as tumoral IDO1 expression were lower in patients with ER-positive compared to ER-negative tumors and an inverse relationship between IDO1 and estrogen receptor mRNA was observed across 14 breast cancer data sets. Analysis of whole genome bisulfite sequencing, 450k, MassARRAY and pyrosequencing data revealed that the IDO1 promoter is hypermethylated in ER-positive in comparison to ER-negative breast cancer. Reduced induction of IDO1 in ER-positive breast cancer cells was also observed in human breast cancer cells. IDO1 induction was enhanced upon DNA demethylation in ER-positive but not in ER-negative cells and methylation of an IDO1 promoter construct reduced IDO1 expression, suggesting that enhanced methylation of the IDO1 promoter suppresses IDO1 in ER-positive breast cancer. Taken together our results show that IDO1 is regulated by DNA methylation and highly expressed in ER negative breast cancers such as basal-like tumors, suggesting a possible benefit of treating patients of this subgroup with an IDO1 inhibitor.

Longitudinal analysis of cytokine profiles in community-acquired pneumonia

CAPSyS

Presenting Author: Maciej Rosolowski

Rosolowski M, Ahnert P, Kirsten H, Loeffler M, Suttorp N, Kiehntopf M, Scholz M

IMISE, Medical Faculty, University Leipzig; Department of Infectious Disease and Respiratory Medicine, Charité - University Medicine Berlin; Integrated Biobank Jena (IBBJ) and Institute of Clinical Chemistry and Laboratory Diagnostics, Jena University Hospital

Factors influencing the clinical course of community-acquired pneumonia (CAP) are still incompletely known. Some patients recover quickly, whereas others develop severe sepsis requiring intensive care and high risk of mortality. Inflammatory response of the host is one of the factors linked to the severity of CAP. In the PROGRESS project, 1,800 CAP patients were collected and studied for four days after admission to the hospital. The assessments include, among others, clinical parameters of organ function summarized by the SOFA score (sequential organ failure assessment), clinical outcomes and levels of 10 cytokines measured by ELISA (available for N=400 patients). We performed time series analysis of these data asking what are the associations among the cytokines and between the cytokines and the clinical outcome parameters of the patients at the same day and over time. An answer to this question is relevant for systems-biological modeling of the immune response in CAP. The challenges in the analysis included: 1) short time series (T=4), 2) patient-specific levels of the cytokines, 3) patient-specific slopes of the trajectories over time, 4) within-patient contemporaneous correlation between the errors. We present first results of the analysis and describe a way in which we attempted to solve the difficulties of estimating lagged associations in our time series data. The methods that we used included methods known from econometrics (dynamic panel models) and psychology (cross-lagged panel models) which, to our knowledge, have not been widely used for analyzing biomedical data.

Profiling tumor transcriptome, urine metabolome and plasma lipidome of Sorafenib treated HCC Patients : a Multi-omics view to understand resistance mechanisms.

Multiscale HCC

Presenting Author: Mohamed Ali Jarboui

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Hepatocellular carcinoma (HCC) is the most common primary liver tumor responsible for about 90% of liver cancers. Globally, HCC is the second leading cause of death within cancer patients. Sorafenib is a small, orally available molecule identified through serial modification of commercially available Raf kinase inhibitor, GK-00687. It has a multikinase inhibitory action and a therapeutic activity against several solid tumors. Recent clinical trials indicate a limited survival benefit in HCC patients treated with Sorafenib. Nevertheless, the mechanisms of therapy response and resistance remain unclear. Therefore, an integrative view of Sorafenib treated patients response is needed in order to identify possible resistance pathways that could help to predict therapy response at a systematic level. In our investigation, we analysed tumors transcriptome, NMR based urine metabolites and plasma lipidome of HCC patients following Sorafenib treatment. Patients were classified in responders and non-responders by a clinical expert panel. Our transcriptomic analysis revealed that the activation pathway of LXR plays a major role in therapy mechanism. Furthermore, by investigating the urine metabolome, we identified metabolites that correlate with sorafenib response level. Moreover, plasma lipoproteins analysis suggests a strong link between non-response or secondary resistance and the levels of HDL and LDL. Overall, our investigation provides a global overview of mechanisms that possibly correlates with HCC patients response to Sorafenib treatment and bring new insights toward personalized patient-tailored cancer therapy. Therefore, combinatory Omics profiling could be used to predict the cancer treatment outcome and to design a more effective targeted therapy.

Cytokine X* is a component of a pathway leading to allograft damage and an early indicator of poor graft function in patients after kidney transplantation (* Patent application in preparation)

e:Kid

Presenting Author: Ellen Witte

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Long-term graft function is the critical issue after kidney transplantation (KTx). Knowledge about the molecular pathways leading to poor allograft function and markers for early detection of concerned patients are the crucial steps to overcome this issue. In a systems medicine-based approach, epidemiological and clinical parameters were collected and more than 50 parameters (serum proteins and metabolites, urine proteins, blood cell profiles and transcriptional and epigenetic signatures) were quantified in up to 172 kidney allograft recipients at different time points after KTx. Graft function was assessed as glomerular filtration rate (GFR), with ≥ 45 ml/min as a cut-off for sufficient function. To identify pathways associated with long-term allograft damage, correlations between parameter levels quantified as early as 2 weeks post KTx and 1-year GFR were calculated. Among 8 identified significant relationships, serum cytokine X (CX), whose levels were clearly increased compared to healthy donors, showed the strongest negative GFR association (P=0.000). In an attempt to identify further elements of the CX pathway, correlation between CX levels and those of all other parameters revealed strongest relationship with endostatin (P=0.000), angiogenin (P=0.010), IL-19 (P=0.004), and sST2 (P=0.020) levels, suggesting a role of CX in angiogenesis and mast cell activation. In vitro investigations are ongoing to prove these assumptions. The GFR-predictive power of 2-week CX levels was confirmed by respective single value ROC curve (AUC: 0.74). Balanced accuracy for prediction of insufficient GFR was 0.71, with a CX cut-off level being 2,133 pg/ml. Combination with up to 3 other markers from distinct pathways further increased the predictive value of CX, as deduced from comparative regression-based classification analyses. Our study suggests that in KTx patients the CX pathway plays a harmful role and may serve as an early marker of graft damage and a new therapeutic target.

Increased mesolimbic cue-reactivity in carriers of the mu-opioid-receptor gene OPRM1 A118G polymorphism predicts drinking outcome: a functional imaging study in alcohol dependent subjects

SysMedAlcoholism

Presenting Author: Falk Kiefer

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The endogenous opioid system is involved in the pathophysiology of alcohol-use disorders. Genetic variants of the opioid system alter neural and behavioral responses to alcohol. In particular, a single nucleotide polymorphism rs1799971 (A118G) in the mu-opioid receptor gene (OPRM1) is suggested to modulate alcohol-related phenotypes and neural response in the mesocorticolimbic dopaminergic system. Little is known about the clinical implications of these changes. The current study investigated the relationship of genotype effects on subjective and neural responses to alcohol cues and relapse in a sample of abstinent alcohol-dependent patients. Functional magnetic resonance imaging (fMRI) was used to investigate alcohol cue-reactivity and drinking outcome of 81 abstinent alcohol-dependent patients. G-allele carriers displayed increased neural cue-reactivity in the left dorsal striatum and bilateral insulae. Neural responses to alcohol cues in these brain regions correlated positively with subjective craving for alcohol and positive expectations of alcohol's effects. Moreover, alcohol cue-reactivity in the left dorsal striatum predicted time to first severe relapse. Current results show that alcohol-dependent G-allele carriers' increased cue-reactivity is associated with an increased relapse risk. This suggests that genotype effects on cue-reactivity might link the OPRM1 A118G risk allele with an increased relapse risk that was reported in earlier studies. From a clinical perspective, risk-allele carriers might benefit from treatments, such as neuro-feedback or extinction-based therapy that are suggested to reduce mesolimbic reactivity.

A transdiagnostic investigation of cognitive control during reward processing

IntegraMent

Presenting Author: Kristina Otto

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Background: Altered reward network (RN) activity has repeatedly been reported in psychiatric patients (Hägele et al., 2015), but mechanisms remain largely unknown. A recent theory postulates that the capacity of the fronto-parietal control network (FPN) is compromised in psychiatric conditions (Cole, et al., 2014), which might contribute to domain-specific deficits, such as aberrant reward processing. Following a transdiagnostic approach, we studied patients with schizophrenia (SZ, N=20), bipolar (BD, N=25), major depressive (MD, N=28), and autism spectrum disorder (ASD, N=22), as well as healthy controls (N=92) during reward anticipation. We expected altered activation and connectivity profiles of the RN and FPN across groups and tested whether disorder severity was predictive of FPN-alterations.

Methods: fMRI data were analyzed using standard processing routines (SPM12) and subjected to a full factorial model for group-level inference. Interactions between the RN and FPN were assessed using seed-based connectivity.

Results: All disorder groups except MD revealed reduced vST responses during reward anticipation (pFWE<.05, small volume correction (SVC)). Within the FPN, pronounced hypoactivation was observed in BD patients (pFWE<.05, wb), although smaller alterations were also evident in other patient groups. In addition, we observed reduced connectivity within the FPN and between the FPN and RN (pFWE<.05, SVC), with several disorder-specific differences. In addition, FPN activation in key regions of the FPN were related to symptom severity across groups (p<.05).

Conclusion: This study points to altered neurobiological mechanisms in reward processing across diagnostic boundaries. Differences were not limited to the RN, but included key regions of the FPN. Our findings highlight the potential of investigating interactions of large-scale brain systems in order to improve our understanding of pathophysiological mechanisms underlying psychiatric conditions.

Pre-mapping Networks for Brain Stimulation (PreNeSt)

PreNeSt

Presenting Author: Tracy Erwin-Grabner

Tracy Erwin-Grabner, Aditya Singh, Grant Sutcliffe, Sarah Wolter, Roberto Goya-Maldonado

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Repetitive transcranial magnetic stimulation (rTMS) has quickly become a well-known option for the treatment of depressive disorders, although its effect on brain networks is not yet fully understood. It can be assumed that individual variations exist in the spatial distributions of these networks and as such, a personalized rTMS approach could better maximize treatment response. To this end, in the initial phase of the PreNeSt project, fMRI is used to identify individual brain networks and optimal regions for stimulation in healthy subjects. Next, a neuronavigation system is used to precisely target these regions of interest for an individualized TMS application. A follow-up fMRI is completed immediately after the TMS stimulation to assess the potential reconfiguration of these networks. The analysis will use both static and dynamic connectivity methods to look for differences between functional connectivity of networks during resting-state fMRI, both pre and post rTMS stimulation and including both active and sham stimulation conditions. Additionally, 3 rs-fMRI time points are used post stimulation to assess rTMS induced local and global connectivity changes over time. In the second phase of the study, initial insights gained regarding the reconfiguration of these networks will be used to further assess potential changes within subjects who are acutely depressed. The translational research of the PreNeSt project aims to further promote understanding of the impact of individualized, network-based rTMS on brain network configurations, with the long-term goal of better informing and supporting a personalized medical approach for the treatment of mood disorders.

Time lapse of individualized repetitive transcranial magnetic stimulation effects on resting state functional connectivity of healthy brains

PreNeSt

Presenting Author: Aditya Singh

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Numerous studies have suggested that a single session of repetitive transcranial magnetic stimulation (rTMS) is effective at manipulating the brain's functional connectivity [1]. However, to date no studies have explored the relationship between the effects of the stimulation on functional connectivity and the elapsed amount of time post-rTMS. Furthermore, while it is possible to manipulate functional connectivity by stimulating at several accessible cortical targets, the DLPFC as an rTMS target is of particular importance due to its therapeutic use in the alleviation of depressive symptoms. To detect differences in effects of rTMS induced targeted at the left DLPFC as a function of elapsed time after stimulation, we recruited healthy volunteers for three experimental sessions. In the initial session, the resting state (rs)-fMRI scan is utilized to select the strongest node of the fronto-parietal network, which also anti-correlates with the anterior cingulate cortex of the default mode network, which then becomes the target for individualized rTMS intervention [2]. The next two sessions, at least a week apart, involve either real or sham rTMS intervention delivered using real time neuronavigation. One pre-rTMS rs-fMRI session and three sequential post-rTMS rs-fMRI sessions (upon completion of rTMS) are acquired. The data is analyzed for differences in functional connectivity during resting state, both between the three rs-fMRI scans acquired post-rTMS and between the pre-rTMS and post-rTMS resting state scans, to measure how long the rTMS effects are sustained and which resting state networks are involved over time. Additionally, we also aim to utilize the rs-fMRI scan from the first session and the two pre-rTMS rs-fMRI scans from next two sessions to test the stationarity of target selection across sessions [3]. References 1. Fox et al. (2012), NeuroImage 62. 2. Fox et al. (2012), Bio. Psych. 72(7). 3. Fox et al. (2013), NeuroImage, 66.

Dynamic functional connectivity analysis of the effects of targeted repetitive transcranial magnetic stimulation

PreNeSt

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Grant Sutcliffe, Aditya Singh, Tracy Erwin-Grabner, Sarah Wolter, Roberto Goya-Maldonado

University Hospital Goettingen

Repetitive transcranial magnetic stimulation (rTMS) is a safe, tested technique of brain stimulation, and rTMS targeting the left dorsolateral prefrontal cortex (DLPFC) has been successfully used to treat major depressive disorder. Analysis of brain connectivity with resting-state fMRI has revealed that rTMS affects connectivity within and between the functional networks of the brain. Previous studies have measured the effects of TMS on resting state connectivity using “static” analysis, averaging correlations over the entire resting-state scan period. However the pattern of correlations during the resting state is not static, and information can potentially be gained with “dynamic” analysis, which measures connectivity at multiple timepoints during the scanning period. The effect of rTMS on dynamic brain functional connectivity during the resting state has not yet been studied. We will use individualized rTMS targeting methods and dynamic connectivity analysis with a placebo-controlled crossover experimental design to explore how 10Hz rTMS to the left DLPFC influences the interaction of functional networks during the resting state. rTMS targets will be defined using independent component analysis applied to resting state data. Connectivity matrices will be created by correlating activity across functionally-defined regions of interest, and sliding windows will be used to create time series of connectivity maps. Data will then be analyzed with both static and dynamic connectivity methods, including the use of clustering algorithms to determine discrete recurring global connectivity states in the time series. By using individualized targeting to increase stimulation efficacy and reliability and by evaluating dynamic changes we aim to discover how rTMS modifies the spatial and temporal organization of interactions between functional networks, and how these effects persist and vary across individuals.

Ethical issues of Molecular Tumor Boards

DASYMED

Presenting Author: Christoph Schickhardt

Christoph Schickhardt, David Merry, Eva C. Winkler

Nationales Centrum für Tumorerkrankungen (NCT), Medizinische Onkologie, Universitätsklinkum Heidelberg

In oncology, Molecular Tumor Boards (MTBs) play a key role in delivering rationales for NGS- and other omics-based targeted therapies. MTBs can be considered as pioneering the application of systems medicine approaches in the clinic. Due to their innovative and experimental approaches, they also raise several ethical issues that need to be addressed. In our talk we will proceed in three steps. First, we will propose a definition of MTBs and highlight the features of MTBs which are of particular normative relevance such as their scientific and methodological complexity and interdisciplinarity. In a second step, we will analyse the most pressing ethical and governance issues of MTBs. A major concern stems from the fact that a patient's treating physician is usually unable to adequately understand and autonomously assess the scientific reasoning at the basis of a MTB's treatment recommendation and that the MTB is, as such, no approved clinical unity or service. Can treating physicians be held responsible for the evidence supporting a MTB's treatment recommendation nonetheless? How should responsibilities for MTB treatment recommendations be distributed? Further issues regard compatibility of non-discrimination requirements and research rationales in recruiting patients for MTBs, and justification and sustainability of costs for the patient and the health care system. In a third step, we will propose measures to adequately address these concerns. One of the solutions we propose is a model of a chain of specific responsibilities based upon reasonable trust. In order to allow the treating physician to trust the MTB recommendation, there is need for a qualified member of the MTB, for instance a translational oncologist, to take primary responsibility for the MTB's recommendation towards the treating physician while, at the same time, making sure that the single MTB members' contribution to the recommendation meet requirements of trust and high quality.

Genomic High-Throughput Data in Clinical Applications: Infrastructural, Ethical, Legal and Psychosocial Aspects

Genoperspektiv

Presenting Author: Nadine Umbach

Nadine Umbach (1), Tim Beißbarth (2), Gunnar Duttge (3), Laura Flatau (4,5), Jessica Kuhn-Aldea (3), Julia Perera Bel (2), Thomas G. Schulze (5), Mark Schweda (6), Julian Trostmann (1), Alexander Urban (6), Anja Zimmermann (3), Ulrich Sax (1)

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Increasingly effective high-throughput pipelines allow sequencing of the human genome within hours. At the cusp of the clinic, it is necessary to understand restrictions and potentials in the context of health and disease. Within the GenoPerspectiv consortium, we address fundamental questions spanning from ethical, psychosocial, and legal issues, but also aspects with regard to infrastructures, data management, and reporting strategies. Finally, we suggest ways to overcome them. Moral attitudes, concerns, and demands of health care professionals, patients, and their relatives were explored and analyzed by means of qualitative social-empirical research. In parallel, a large-scale survey (n=1000) was conducted to analyze intrapersonal, interpersonal, and external factors. Moreover, we have addressed the implementation of a seamless pipeline from biomaterial collection over sequencing to reporting in molecular tumor boards. Finally, legal rights and obligations have been analyzed especially the German Gene Diagnostic Act, protection of data privacy, and health insurance laws. Guidelines and practical recommendations on how to deal with genomic high-throughput sequencing and corresponding data were formulated and discussed with experts and lay people addressing the following topics: i) patient autonomy, informational self-determination, doctor`s professional role, and responsibilities; ii) test methodologies, data quality, and reporting strategies in molecular tumor boards; iii) integration, analysis, and interpretation of data; iv) collaborative working interactions, interdisciplinary education in clinical genomics, and communication of clinical information; v) refinements of regulations and laws for practical application.

TCR NGS based evidence for differential diagnosis and personalized therapy in BKV Nephropathy

e:Kid

Presenting Author: Ulrik Stervbo

Ulrik Stervbo, Thomas Klein, Mikalai Nienen, Richard Viebahn, Timm H Westhoff MD*, Nina Babel MD*

US, MN, TW, NB: Center for Translational Medicine, Medical Clinic I, Marien Hospital Herne, University Hospital of the Ruhr-University Bochum, Hölkeskampring 40, 44625 Herne, Germany // TK, RV: Department of Surgery, Knappschaftskrankenhaus Bochum, University Hospital of the Ruhr-University Bochum, In der Schornau 23-25, 44892 Bochum, Germany

BKV nephropathy (BKVAN) is a disease in 10% of renal transplant recipients which might lead loss of the graft in up to 80% of the cases. Current the diagnosis is based on assessment of BKV viral load in serum with assessment of inclusion bodies by kidney biopsy for definitive diagnosis. In case of identified BKVAN, the principle treatment is to decrease or alter the immunosuppressive regimen. However, the pathological features of BKVAN overlap with those of acute cellular rejection, where decrease of immunosuppression is detrimental. Confronted with this vexing problem, we obtained a renal biopsy from a German male, transplanted with a kidney from a close living relative. By way of magnetic bead enrichment of activated T-cells we isolated T-cells reactive to BKV and donor cells in a direct and indirect fashion. Together with the fresh renal tissue, the activated T-cells were prepared for next-generation sequencing (NGS) of the T-cell receptor (TCR). We isolated T-cells in all three activation modi, which indicates an expansion of virus as well as donor specific T-cells in the patient, and underpins the complexity of diagnosis. When we compared the TCR repertoires of activated peripheral T-cells to those in the biopsy, we observed a distinct and strong presence of BKV specific T-cells in the transplant. This clearly excluded acute cellular rejection and allowed confident decrease of the immunosuppressive regimen. Identification of the specificity of tissue infiltrating T-cells by TCR NGS is a valuable technique for differential diagnosis and personalized therapy .

How to report somatic variants in molecular tumor boards

Genoperspektiv

Presenting Author: Júlia Perera-Bel

Júlia Perera-Bel1, Barbara Hutter2, Christoph Heining3, Annalen Bleckmann1, Martina Fröhlich2, Stefan Fröhling3,4, Hanno Glimm3,4, Benedikt Brors2 and Tim Beißbarth1

1University Medical Center Göttingen, 2German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), 3National Center for Tumor Diseases (NCT) and German Cancer Research Center (DKFZ), 4German Cancer Consortium (DKTK)

The understanding of complex diseases, such as cancer, has furthered with the improvements of high-throughput technologies e.g., next-generation sequencing. However, advances in technology platforms and bioinformatic tools contrast with the scarce implementation of cancer genomics in clinical practice. One reason for this situation is that pathologists and oncologists have to face thousands of genomic alterations and unravel their clinical relevance. Accordingly, the scientific community has claimed the need of a comprehensive knowledge database as well as decision support platforms for the interpretation and reporting of genomic findings in clinical practice e.g., in molecular tumor boards. Towards this end, we have developed a framework for interpreting and reporting genomic data relying entirely on public knowledge. The method focuses on actionable variants - genomic alterations that predict drug response. In particular, gene-drug associations are classified according the stage of development of the drug (approved, clinical trials or pre-clinical studies) and the cancer type for which the predictive association exists. We tested the framework on the Pan-Cancer dataset from The Cancer Genome Atlas (3184 samples from 12 cancer types) and 11 patients from the NCT MASTER trial – whose treatment decisions where based on genomic data. We showed that the reporting method is able to 1) find actionable variants in the majority of the patients and, 2) reproduce experts' treatment suggestions in the MASTER dataset. We present a proof-of-concept for a method to report treatment options based on the genomic profile of the patient. It is designed as a supporting tool for all clinicians, biologists and bioinformaticians working with genomic characterization of patients in clinical routine and facing complex decisions regarding treatment options.

Exhibitors

Company Lunch Talks

Olink: A precision proteomics solution for targeted human protein biomarker discovery

Presenting Author: Martin Lundberg

Martin Lundberg, Leonhard Pollack, Erika Assarsson

Olink Proteomics

Identifying relevant protein biomarkers helps to bring new insights into disease processes, improve disease detection, and contribute to a better understanding of pathophysiology. Using multiple proteins that form a signature is more powerful and reliable than looking at a single protein, but this requires studies that examine many different proteins simultaneously, in large numbers of human samples. Olink's precision proteomics solution enables such studies by providing sensitive, high-multiplex immunoassays that do not compromise on data quality. We will show how our dual-recognition, DNA-coupled Proximity Extension Assay (PEA) technology overcomes the cross-reactivity problems normally associated with multiplexed immunoassays, providing exceptional readout specificity. Details of the thorough validation procedures we apply to all of our assays will be presented, along with the design strategy behind our disease-focused biomarker panels, each of which measures 92 different proteins simultaneously, using just 1 µL of almost any type of biological sample.

Martin Lundberg, Chief Technology Officer at Olink Proteomics.

Works cross-functionally with development of novel technologies, products and analytical methods within the area of targeted proteomics. Is a co-inventor of the Proximity Extension Assay (PEA) used for highly multiplexed protein detection. Has a strong technological focus with a background in molecular biotechnology engineering at Uppsala University.

Clinical Implementation of Pharmacogenetics

Presenting Author: Ingolf Cascorbi

Institute of Experimental and Clinical Pharmacology, Christian Albrechts University Kiel

HMG Systems Engineering GmbH

Interindividual differences of drugs efficacy and safety are a major problem in pharmacotherapeutic approaches. Such differences are partly on the disregard for comorbidities or organ dysfunction, drug-drug interactions as well as genetic causes. Recently it was shown that germ line variants in only 20 genes influence the effect of 80 drugs, corresponding to 7% of the drugs prescribed in the USA, which alone account for 18% of the prescriptions. Such pharmacogenetic features may affect pharmacodynamics, pharmacokinetics, and the risk of hypersensitivity reactions. Currently however, precision therapy in oncology focusses in particular on somatic variants in tumor tissue within the successful framework of companion diagnostics. To this end, the US-based Clinical Pharmacogenetics Implementation Consortium (CPIC) has developed more than 35 recommendations that provide evidence-based prescription changes in the presence of certain hereditary genetic traits. To utilize such information, clinical decision support algorithms may be extremely helpful for prescribers. However, to consider also further sources of variability, such as co-administration of drugs, nutrition and e.g. kidney function, further elaborated algorithm are required, automatically analyzing health care records and transform data into simple clinical decision reports, allowing prescribers to optimize individual drug-therapy.In the future, pharmacogenomics will refer not only to frequent germline variants, but to complex molecular properties, including consequences of multiple (even more rare) genetic variation, as well as the influence of epigenetics on gene expression and function requiring advanced DNA sequencing and bioinformatic tools.

Ingolf Cascorbi, Institute of Experimental and Clinical Pharmacology, CAU Kiel

Ingolf Cascorbi is professor of pharmacology at the University of Kiel, Germany and director of the Institute of Experimental and Clinical Pharmacology, University Hospital Schleswig-Holstein, Campus Kiel. He graduated in biochemistry in 1985 and in medicine in 1992 at the Free University of Berlin. He earned a PhD in biochemistry in 1989, and an MD in 1999. After being research associate at the Free University Berlin and later at the Charité Berlin, he received a board certification in clinical pharmacology. In 2000, he was appointed as associate professor of pharmacology and toxicology at University of Greifswald. In 2004, Ingolf Cascorbi was appointed to Kiel. His research interests are in pharmacogenomics and -epigenomics, in particular of drug efflux transporters, drug metabolism and mechanisms of drug resistance as well as genetic factors of complex diseases, neuropathic pain research, and clinical studies. He has published more than 220 scientific papers. Ingolf Cascorbi is currently Vice Dean of Education of the Medical Faculty and serves as member of several boards of scientific societies and authorities, as well of scientific journals.

Experiences from the 2017 e:Med Summer School SEEDED

Presenting Author: Karsten Rippe, DKFZ & Heidelberg University, see page39

How advancements in Next Generation Sequencing support Functional Genomics Research

Presenting Author: Matthias Prucha, Illumina

Illumina

This year e:Med has organised the SEEDED Summer School in Heidelberg, supported by Illumina. The Summer School covered practical aspects of RNA Sequencing, ATAC Sequencing and Whole-genome Bisulfite Sequencing, from sample to interpretation. In our workshop Dr. Karsten Rippe will report on the experiences and outcome of the Summer School, and discuss how this concept can be used for planning of future Summer Schools. In the second half of the workshop we will cover new developments in single cell sequencing, gene regulation and technology.

Dr. Matthias Prucha
District Marketing Manager – Central Europe, Illumina

After studying microbiology and biochemistry at TU Braunschweig, I did my PhD and post-doc characterizing enzymes essential for the degradation of chlorinated aromatic organic pollutants. My industry career I started in sales, support and marketing of bioimaging instruments for the German distributor of Fujifilm, before I joined Affymetrix for 10 years. Here I had a support role, but added collaborative and marketing projects, became European specialist for whole transcriptome gene expression/ alternative splicing detection with exon arrays and gene regulation studies using tiling arrays – today regarded as precursor technology for NGS. In parallel I was European genotyping specialist for automated SNP detection in population genetics before I joined Partek (software company) 2010 as business development & support manager for Europe. Here I formed the European support team but was also directly involved in the development of data analysis tools for demanding molecular biology applications, especially for NGS data.

Since 2013 I joined Illumina as regional marketing manager in Germany, Switzerland and Austria to run trade shows, own events, projects and campaigns to raise awareness and generate demand. Market- and business development projects are tied in with this closely and collaborations with KOLs in central Europe.

Gene Expression Profiling of Blood Samples: QuantSeq 3' mRNA-Seq Library Preparation with Globin Reduction

Presenting Author: Lukas Paul

Lexogen GmbH

Lexogen's QuantSeq technology provides a fast, cost-efficient protocol for generating strand-specific NGS libraries either close to the 3' end of polyadenylated RNAs (QuantSeq 3' mRNA-seq) or targeting user-defined sets of RNAs (QuantSeq-Flex). The versatile kit family also enables detection and quantification of poly(A) sites as well as automated screening of (differential) gene expression in high-throughput experiments with thousands of samples. In all cases, users benefit from low input requirements (starting from 100 pg total RNA), accurate quantification also of degraded and FFPE-sourced RNA and a free, cloud-based gene expression data analysis. Lexogen now has further developed this workflow for the analysis of blood samples. The QuantSeq 3' mRNA kit is poly(A)-selective and therefore, ribosomal RNAs are not present in the final NGS libraries. However, in blood samples globin mRNA levels are very high and hence most NGS reads would map to only few genes. The 3' tag profiling approach of QuantSeq allows the use of stopper oligos that essentially exclude globin RNAs from entering the library preparation. In this lunch talk, we will present results of this highly cost-effective and efficient reduction method.

Lukas Paul

Lukas Paul worked in academia on RNA biology projects from catalysis to RNA stability, RNA folding and RMA-protein interactions before joining Lexogen in 2008 to develop RNA-Seq protocols. He then moved on within the company to manage custom RNA sequencing projects and to develop RNA spike-in standards. Dr. Paul now promotes "scientific affairs" with Lexogen, which entails presentations of the technologies and the portfolio, consultation on and development of RNA-seq projects and the initiation of R&D-based collaborations.

Exhibitors

Exhibitor stands

We thank our sponsors for the kind support of the e:Med Meeting 2017:

Olink

Through our dedication to innovation, quality, rigor and transparency, Swedish company Olink Proteomics provides outstanding products and services for targeted human protein biomarker discovery. We help scientists get answers quickly and confidently through robust, multiplex biomarker analysis. Olink immunoassay panels enable rapid, high-throughput analysis, with exceptional data quality and minimal sample consumption. Using just 1 µl of sample, 92 biomarkers are assayed simultaneously, with up to 96 samples run per panel. Our Proximity Extension Assay (PEA) technology enables this high level of multiplexing, as this dual recognition, DNA-coupled method provides exceptional readout specificity. Disease area or biological process-focused panels have both validated and exploratory biomarkers, and our rigorous assay validation data is freely available. Choosing either ready-to-use kits or our Analysis Service, customers get high quality data and rapid high-throughput analysis that makes the most effective use of their precious samples.
www.olink.com

HMG Systems Engineering GmbH

HMG's vision - "the appropriate drug with the right dose at the right time for the right patient" HMG Systems Engineering GmbH (HMG) located in Fürth (Bavaria), Germany is a small to medium-sized enterprise focused on IT-based innovations. We have 34 employees from eight different nations who work together to translate innovations into reality. Business activities range from offering comprehensive IT based systems engineering services for well-known multi-national companies up to our medical experts and decision support system - the PGXperts platform. Since 2014 we have been developing this platform to facilitate "precision medicine". It enables physicians to tailor medication more precisely providing additional information based on the individual patients pharmacogenetics profile, its clinical consequences and a drug interaction check. A clinical pilot (100 patients) has been performed and a drug interaction app including PGx related information will be introduced in September.
In 2016 HMG was awarded as one of the Top 100 (top100.de) most innovative SMEs in Germany and our PGXperts Platform was placed second at the PerMediCon (congress for personalized medicine), December 2016.
www.hmg-systems-engineering.com

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Illumina

Illumina is a leading developer, manufacturer, and marketer of life science tools and integrated systems for large-scale analysis of genetic variation and function. These systems are enabling studies that were not even imaginable just a few years ago, and moving us closer to the realization of personalized medicine. With rapid advances in technology taking place, it is mission-critical to offer solutions that are not only innovative, but flexible, and scalable, with industry-leading support and service.

We strive to meet this challenge by placing a high value on collaborative interactions, rapid delivery of solutions, and meeting the needs of our customers.

Our customers include a broad range of academic, government, pharmaceutical, biotechnology, and other leading institutions around the globe.

www.illumina.com

Lexogen

Lexogen is a transcriptomics and next-generation sequencing company based in Vienna, Austria. Our product portfolio offers solutions for diverse RNA analysis applications and includes kits for whole transcriptome sequencing, expression profiling, small RNA sequencing, metabolic RNA sequencing, full-length cDNA amplification, RNA extraction, RNA enrichment and depletion, spike-in RNA controls, and software for RNA-Seq data analysis.

www.lexogen.com

LIFE & BRAIN GmbH

LIFE & BRAIN GmbH is a biomedical and neurscientific technology platform founded in 2002 by the University of Bonn and Bonn Medical Center.

LIFE & BRAIN's mission is to close the gap between academic research and business to develop new strategies for the diagnosis and therapy of nervous system disorders. As an innovation center in the field of biomedicine, LIFE & BRAIN brings together expertise in genomic research, transgenic animals, stem cell biology and neurocognition to deliver novel products for disease modeling, early diagnosis, compound development and tissue regeneration.

www.lifeandbrain.com

We thank our sponsors for the kind support of the e:Med Meeting 2017:

GeneWerk GmbH

Based on more than two decades of expertise in the field of gene therapy, gene editing and immunotherapy GeneWerk GmbH was founded 2014 in the biotechnology metropolitan area Rhein-Neckar, Heidelberg, Germany. Our business partners appreciate our worldwide unique experience in assessing vector safety and efficacy in gene therapy and immune repertoire studies as well as assistance in associated regulatory demands. Thereby we provide highly sensitive technical platforms and bioinformatics to determine fusion sequences adjacent to known DNA or RNA fragments in minimal tissue samples. Applications include clonality and safety of viral vectors in gene therapy, on-target specificity of designer nucleases, immune repertoire studies in T and B cells and Next Generation Sequencing. Operating within several consortia (e.g. SCIDNET, CRACK IT) allows us to focus on our mission - to improve the safety of novel gene therapy products for patients and help reducing the reliance on animal models.
www.genewerk.com

Promega

With more than 1.400 employees and a portfolio of more than 3.500 products Promega belongs to one of the largest global acting Life Science research companies. Originally founded in 1978 in Madison, Wisconsin, USA, Promega develops and manufactures products covering the fields of genomics, protein analysis and expression, cellular analysis, drug discovery and genetic identity. Promega is a global leader in providing innovative solutions and technical support to life scientists in academic, industrial and government settings. The company has branches in 16 countries and more than 50 global distributors serving 100 countries.
www.promega.de

GATC Biotech

Founded in 1990, GATC Biotech has established itself as a leader in DNA and RNA sequencing. More than 10,000 researchers worldwide rely on the company's services for processing any number of samples from any kind of starting material. GATC Biotech offers all leading sequencing technologies in its own laboratories. The company's proprietary workflows deliver ready-for-diagnostics results backed by stringent quality accreditations. From Sanger to next generation sequencing, GATC Biotech offers unmatched flexibility to customers interested in any kind of genomics such as transcriptome, epigenome, exome or whole genome analysis.
GATC Biotech's oncology-related services include the world's most comprehensive liquid biopsy-based assays, GATCLIQUID. The services offer whole-exome, targeted or single gene sequencing of cell-free DNA for tumour mutation profiling that can help improve patient outcomes.
www.gatc-biotech.com

National Institute for Science Communication (NaWik)

At the National Institute for Science Communication (NaWik) scientists, students and communicators learn the basics of good science communication. Researchers will be able to communicate the objectives, methods, problems and results of their work in a way that makes them understandable to changing target groups - and to use the respective media skillfully.

For this purpose, NaWik offers tried-and-tested training and further education formats that offer the participants a high utility value for their daily work. The seminars are led by experienced lecturers and can be booked nationwide.

The National Institute for Science Communication was founded in 2012 as a non-profit limited liability company. Shareholders are the Klaus Tschira Foundation and the Karlsruhe Institute of Technology.

www.nawik.de

European Association of Systems Medicine e.V. (EASyM)

The European Association of Systems Medicine e.V. (EASyM) is a charitable association open to everyone with an interest in Personalized, Predictive, Preventive and Participatory (P4) Systems Medicine. EASyM was initiated as the legacy of CASyM - a European Commission funded FP7 Coordination and Support Action (www.casym.eu). EASyM will maintain, expand and implement the assets built up by CASyM; continuing the long-term vision of establishing Systems Medicine-based practices in the European healthcare and biomedical research environment.

EASyM is promoting the integration of bioinformatics, computational modeling and mathematics with biological, molecular and clinical sciences for improved extraction of useful and actionable information of biomedical data. EASyM provides a platform for those who are interested in practicing P4 Systems Medicine and those who are further developing, promoting and expanding Systems Medicine approaches.

www.easym.eu

German Network for Bioinformatics Infrastructure (de.NBI)

The 'German Network for Bioinformatics Infrastructure' (de.NBI, www.denbi.de) has been initiated by the Federal Ministry of Education and Research (BMBF) to meet the bioinformatic challenges in modern life sciences due to the rapid technological progress in analytical areas such as sequencing, 'omics' and imaging techniques. These technologies generate huge amounts of data (big data), and thus require the access to well-maintained databases, bioinformatics tools, workflows and computing capacities.

de.NBI develops and maintains almost 100 bioinformatic services and offers training courses in human, plant and microbial research. de.NBI also fosters the de.NBI Cloud to offer the computing power that today's researchers need to cope with the big data challenge. As the German Node in ELIXIR, de.NBI connects the German community with Europe and beyond.

If big data exploitation in life sciences is your topic, come and visit us at our booth!

TMF

TMF (www.tmf-ev.de) is the umbrella organisation for research data infrastructures and collaboration in biomedical research in Germany. It is a platform for interdisciplinary exchange, cross-project and multi-site collaboration – with the aim of identifying and resolving the organisational, legal/ethical and technological issues encountered in today's medical research. It makes a number of resources available free of charge – such as expert opinions, generic concepts, software applications, checklists, practical guides, training, and consulting services. It operates infrastructures such as the German Biobank Registry (www.biobanken.de) or the information portal "ToolPool Gesundheitsforschung" (www.toolpool-gesundheitsforschung.de).

www.tmf-ev.de

e:Med Project Groups

Informatics & Modeling

Organization:
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Prof. Dr. Thomas Höfer
DKFZ Heidelberg, SYSMED-NB
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The Project group **Informatics and Modeling** links scientists contributing to e:Med projects with a background in mathematics, bioinformatics, medical informatics, and others. Dr. Matthias Ganzinger (Heidelberg University, CLIOMMICS) and Prof. Thomas Höfer (DKFZ Heidelberg, SYSMED-NB) lead this project group.

The group addresses issues from the areas of information technology and modelling. Topics of the group include the **IT infrastructure in systems medicine projects**, **data acquisition, and data management** in large-scale projects for ensuring a sustainable and effective usage of data. Further aspects discussed are **data security and data sharing** from an IT point of view. In particular, participants share their approaches in information technology and modeling with the group.

The PG initiated a detailed online survey among the e:Med projects to get an overview of the tools and data used for systems medicine research. The results are available to all e:Med members on the intranet.

The PG organized a focus **workshop on data management** in systems medicine, as result **a "best practice"-paper** was planned. Material from the workshop in Berlin can be found in the members' area of the e:Med web page.

At the e:Med Meeting, on Tuesday, Nov 21, 10:00 - 11:00 am there will be a **follow-up meeting of the group**. We will review the workshop in Berlin and discuss the state of **"best practice"-paper**. Additionally, we will discuss current topics and further **proceedings of the project group**.

e:Med members are very welcome to contact us and join the group.

Data Security & Ethics

Organization:
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Prof. Dr. Ulrich Sax
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Prof. Dr. Marcella Rietschel
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Project group **Data Security and Ethics** deals with data protection, data access, and ethical aspects in relation to research usages of sensitive patient data . The project group is led by Dr. Christoph Schickhardt (NCT Heidelberg, DASYMED) and Professor Dr. Ulrich Sax (University of Göttingen, SysINFLAME), and is supportively advised by Professor Dr. Marcella Rietschel (ZI Mannheim, IntegraMent). The group discusses issues essential for **sharing and publishing of (big) human (Gen)Omics data**, for instance patient consent and information, transfer of data beyond the EU, and withdrawal of data. The group also cooperates with the **TMF groups Data Security and Molecular Medicine** (ITQM and MolMed). Issues of practical relevance for biomedical data driven science are discussed with ethical and legal experts as well as scientists in order to inform and support researchers in practice.

e:Med members are very welcome to contact us and join the group.

Image Processing

Organization:
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The project group **Image Processing** focuses on exchanging scientific experience with a diversity of image processing technologies. Relevant issues are tools and structure for merging the various types of data. An appropriate database for archiving and exchanging different formats and analyses for scientific and clinical data should be identified and adapted to the needs of participating scientists. The PG discussed the possibilities of internal e:Med data exchange, especially of imaging data, and the development and utilization of a joint infrastructure. To identify a suitable **platform for archiving and exchanging data**, requirements were identified and software packages presented that are already in use or planned to be employed.

At the e:Med Meeting, on Wednesday**, Nov 22, 06:45 - 07:30 pm** the next meeting of the **e:Med project group Image Processing** will take place.Content of the short meeting, in particular, will be the **future orientation of the project group**. The agenda includes a review of **previous activities**, **exchange of experiences on Imaging - Projects** and discussion on **further steps** of the project group.

e:Med members are very welcome to contact us and join the group.
We look forward to your active participation to shape the e:Med PG Image Processing based on your needs!

Epigenetics & Sequencing

Organization:

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The project group **Epigenetics & Sequencing** fosters interactions and joint activities of e:Med scientists that apply **deep sequencing methods** to study the **(epi)genome and transcriptome** of disease cells. A list of participating researchers and their expertise with respect to experimental and theoretical methods is available to all e:Med members in the intranet.

The latest activity of the Epigenetics & Sequencing group was the very successful e:Med summer school SEEDED: "Sequencing analysis of epigenetic deregulation in disease". See information and report under www.sys-med.de/SEEDED.

The ongoing activities of the Epigenetics & Sequencing group center around the following areas: (i) **Support of initiatives** to acquire additional funding that covers sequencing projects in systems medicine studies. (ii) **Exchange of strategies and protocols** for experimental multi-readout data acquisition approaches from a limited amount of patient sample material and the subsequent analysis and integration of the data. (iii) **Development and application of single cell sequencing technologies** within e:Med.

At the e:Med Meeting 2017, the **Project group Epigenetics & Sequencing** is organising the **Satellite Symposium Technological Innovations**.

e:Med members are very welcome to contact us and join the group.

List of e:Med
Systems Medicine Research Consortia

CancerTelSys

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

Coordinator: Prof Dr. Karsten Rippe

Coordinator of subproject				**Subproject**	
Name	First Name	Title	Institution	Nr	Title
Plass	Christoph	Prof. Dr.	DKFZ Heidelberg		
König	Rainer	Prof. Dr.	CSCC, Universitätsklinikum Jena		
Luke	Brian	Dr.	Universität Heidelberg		
Pfister	Stefan	Prof. Dr.	DKFZ Heidelberg		
Sauter	Guido	Prof. Dr.	Universitätsklinikum Hamburg-Eppendorf		Telomere maintenance mechanism (TMM) (epi)genomics and transcriptomics
Simon	Ronald	Dr.	Universitätsklinikum Hamburg-Eppendorf	SP 1	
Rohr	Karl	Prof. Dr.	Universität Heidelberg		
Erfle	Holger	Dr.	Universität Heidelberg	SP 2	Image analysis of cytological TMM-features
König	Rainer	Prof. Dr.	CSCC, Universitätsklinikum Jena		
Luke	Brian	Dr.	Universität Heidelberg		
Rippe	Karsten	Prof. Dr.	DKFZ Heidelberg		
Rohr	Karl	Prof. Dr.	Universität Heidelberg	SP 3	Modeling TMM networks in tumors
Rippe	Karsten	Prof. Dr.	DKFZ Heidelberg		
Erfle	Holger	Dr.	Universität Heidelberg		
Luke	Brian	Dr.	Universität Heidelberg		
Pfister	Stefan	Prof. Dr.	DKFZ Heidelberg		
Plass	Christoph	Prof. Dr.	DKFZ Heidelberg	SP 4	Validation and functional TMM analysis
Erfle	Holger	Dr.	Universität Heidelberg		
Luke	Brian	Prof. Dr.	IMB Mainz		
Rippe	Karsten	Prof. Dr.	DKFZ Heidelberg	SP5	Technology development for TMM classification
Pfister	Stefan	Prof. Dr.	DKFZ Heidelberg		
Luke	Brian	Prof. Dr.	IMB Mainz		
Plass	Christoph	Prof. Dr.	DKFZ Heidelberg		
Rippe	Karsten	Prof. Dr.	DKFZ Heidelberg		
Sauter	Guido	Prof. Dr. med.	Universitätsklinikum Hamburg-Eppendorf	SP6	Clinical application of TMM analysis scheme
Rippe	Karsten	Prof. Dr.	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	First Name	Title	Institution	Nr	Title
Scholz	Markus	Prof. Dr.	IMISE, Universität Leipzig	SP 1	Integrative Genetic Analysis and Biomathematical Modelling of Systemic Inflammation
Suttorp	Norbert	Prof. Dr.	Charité Berlin	SP 2	Deep phenotyping in patients with severe CAP and new analyses in established cohorts
Vera-Gonzalez	Julio	Prof. Dr.	Universitätsklinikum Erlangen	SP 3	Mathematical modelling of pneumonia pathophysiology
Schmeck	Bernd T.	Prof. Dr.	Philipps-Universität Marburg	SP 4	Experimental modelling and validation of pneumonia pathophysiology
Witzenrath	Martin	Prof. Dr.	Charité Berlin		
Löffler	Markus	Prof. Dr.	IMISE, Universität Leipzig	SP 5	Platform for Data-Integration, Communication, Data Mining, and Project Management

CLIOMMICS

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

Coordinator: Prof. Dr. Hartmut Goldschmidt, PD Dr. Dirk Hose

Coordinator of subproject				Subproject	
Name	First Name	Title	Institution	Nr	Title
Knaup-Gregori	Petra	Prof. Dr.	IMBI, Universitätsklinikum Heidelberg	SP 1	IT-Architecture and Multi-level Data Management for Systems Medicine for Multiple Myeloma
Hemminki	Kari	Prof. Dr.	DKFZ Heidelberg	SP 2	Genetic markers predicting side effects, therapeutic response and prognosis in myeloma
Hose	Dirk	PD Dr.	Universitätsklinikum Heidelberg	SP 3	Transcriptomics by RNA-sequencing: Performing and reporting in clinical routine
Seckinger	Anja	Dr.	Universitätsklinikum Heidelberg		
Kopp-Schneider	Annette	Prof. Dr.	DKFZ Heidelberg	SP 4	Combining MRI, SNPs, FISH and GEP/RNAseq in improving risk prediction and treatment decision making
Hielscher	Thomas		DKFZ Heidelberg		

e:AtheroSysmed Systems medicine of myocardial infarction and stroke Coordinator: Prof. Dr. Jeanette Erdmann, Prof. Dr.Heribert Schunkert					
Coordinator of subproject				**Subproject**	
Name	First Name	Title	Institution	Nr	Title
König	Inke R.	Prof. Dr.	Universität zu Lübeck, Institut für Medizinische Biometrie und Statistik		
Müller-Myhsok	Bertram	Prof. Dr.	Max-Planck-Institut für Psychiatrie, Research Group Statistical Genetics		
Erdmann	Jeanette	Prof. Dr.	Universität zu Lübeck, Institut für Integrative und Experimentelle Genomik		Identification of risk alleles and risk profiles
Schunkert	Heribert	Prof. Dr.	Deutsches Herzzentrum München, Klinik für Herz- und Kreislauferkrankungen	SP 1	
Peters	Annette	Prof. Dr.	Helmholtz Zentrum München	SP 2	Multi-scale OMICs analysis for novel pathways of coronary artery disease and ischemic stroke
Söding	Johannes	Dr.	Max-Planck-Institut für biophysikalische Chemie		
Erdmann	Jeanette	Prof. Dr.	Universität zu Lübeck, Institut für Integrative und Experimentelle Genomik	SP 3	Identification of disease-associated gene regulatory networks
Erdmann	Jeanette	Prof. Dr.	Universität zu Lübeck, Institut für Integrative und Experimentelle Genomik		
Engelhardt	Stefan Hanns	Prof. Dr.	Technische Universität München, Institut für Pharmakologie und Toxikologie		SNP-mediated miRNA (dys)regulation in atherosclerosis
Theis	Fabian	Prof. Dr.	Helmholtz Zentrum München	SP 4	
Dichgans	Martin	Prof. Dr. med.	Klinikum der Universität München		
Mann	Matthias	Prof. Dr.	Max-Planck-Institut für Biochemie		PWAS for identification of functional SNPs and key molecules in arterial injury
Schunkert	Heribert	Prof. Dr.	Deutsches Herzzentrum München, Klinik für Herz- und Kreislauferkrankungen	SP 5	
Kuhn	Klaus	Prof. Dr.	Klinikum rechts der Isar der TU München		
Krüger	Bernd	Prof. Dr.	Universität Heidelberg, Universitätsmedizin Mannheim	SP 6	Integration and harmonization of data, translation of results
Schunkert	Heribert	Prof. Dr.	Deutsches Herzzentrum München, Klinik für Herz- und Kreislauferkrankungen	SP 7	Organisation and Coordinaton

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	First Name	Title	Institution	Nr	Title
Babel	Nina	Prof. Dr.	Charité - Universitätsmedizin Berlin	SP 1	Sample management, monitoring of viral infection and virus-specific immunity
Hugo	Christian	Prof. Dr.	TU Dresden	SP 2	Systems medicine approach to personalized immunosuppressive treatment at early stage after Kidney Transplantation
Wolk	Kerstin	Dr.	Charité University	SP 3	Assessment of cytokines, the pivotal messengers in intercellular communication
Sabat	Robert	Dr.	Charité University		
Reinke	Petra	Prof. Dr.	Charité University	SP 4	Sample management, monitoring of viral infection and virus-specific immunity
Sawitzki	Birgit	Prof. Dr.		SP 5	Analysis of peripheral tolerance signature early after transplantation to identify low risk patients
Or-Guil	Michal	Dr.	Humboldt-Universität zu Berlin	SP 6	Management of data communication
Seitz	Harald	Dr.	Fraunhofer Institute for Cell Therapy and Immunology	SP 8	Characterisation of antibody-antigen interactions and adapation on a diagnostic platform
Olek	Sven	Dr.	Epiontis GmbH	SP 9	Epigenetic biomarkers for risk assessment, prognosis, and prediction of post-transplant course upon kidney transplantation
Schuchhardt	Johannes	Dr.	MicroDiscovery GmbH		

IntegraMent

Integrated Understanding of Causes and Mechanisms in Mental Disorders

Coordinator: Prof. Dr. Markus Nöthen

Coordinator of subproject				Subproject	
Name	First Name	Title	Institution	Nr	Title
Nöthen	Markus	Prof. Dr.	Universitätsklinikum Bonn		
Lange	Christoph	Prof. Dr.	Uni Bonn, Genomische Mathematik		
Mattheisen	Manuel	Prof. Dr.	Department of Biomedicine		
Müller-Myhsok	Bertram	Prof. Dr.	Max Planck Institut für Psychiatrie		
Theis	Fabian	Prof. Dr.	Helmholtz Zentrum, München	SP 1	Data integration and systems modeling in mental disorders

IntegraMent

Integrated Understanding of Causes and Mechanisms in Mental Disorders

Coordinator: Prof. Dr. Markus Nöthen

Coordinator of subproject				**Subproject**	
Name	First Name	Title	Institution	Nr	Title
Rietschel	Marcella	Prof. Dr.	Zentral Institut für Seelische Gesundheit		
Rujescu	Dan	Prof. Dr.	Universität Halle		
Binder	Elisabeth	Dr.Dr.	Max Planck Institut für Psychiatrie		
Schulze	Thomas	Prof. Dr.	Ludwig-Maximilians-Universität München	SP 2	Central patient resource and bridging between genotype and phenotype
Degenhardt	Franziska	Dr.	Institute of Human Genetics, University of Bonn		
Cichon	Sven	Prof. Dr.	Universität Basel		
Nöthen	Markus	Prof. Dr.	Universitätsklinikum Bonn	SP 3	Large-scale molecular genetic studies
Meyer-Lindenberg	Andreas	Prof. Dr.	Zentral Institut für Seelische Gesundheit		
Heinz	Andreas	Prof. Dr.	Charité-Universitätsmedizin Berlin		
Walter	Henrik	Prof. Dr. Dr.	Charité-Universitätsmedizin Berlin	SP 4	Transdiagnostic neurocognitive biomarkers for the major psychoses
Grabe	Hans Jörgen	Prof. Dr.	Universität Greifswald		
Schulze	Thomas	Prof. Dr.	Ludwig-Maximilians-Universität München	SP 5	Polygenic risk profiles for major psychiatric disorders in the general population
Fischer	André	Prof. Dr.	Georg-August-Universität Göttingen		
Giese	Armin	Prof. Dr.	LMU Munich		
Kraus	Theo	Dr.	LMU Munich		
Falkai	Peter	Prof. Dr.	LMU Munich	SP 6	Epigenetics and transcriptome plasticity in psychiatric diseases
Wurst	Wolfgang	Prof. Dr.	Helmholtz Zentrum München		
Deussing	Jan	Dr.	Max Planck Institut für Psychiatrie,	SP 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)	SP 8	Interactome networks and perturbed cellular functions in schizophrenia and bipolar disorder
Brüstle	Oliver	Prof. Dr.	Universität Bonn und Hertie-Stiftung	SP 9	Human iPS cell-based neuronal cultures for modeling neuropsychiatric disease

IntegraMent

Integrated Understanding of Causes and Mechanisms in Mental Disorders

Coordinator: Prof. Dr. Markus Nöthen

Coordinator of subproject				Subproject	
Name	First Name	Title	Institution	Nr	Title
Durstewitz	Daniel	Prof. Dr.	Zentral Institut für Seelische Gesundheit	SP 10	Neurodynamic analysis of psychiatric disease mechanisms using computational network models computational network models
Nöthen	Markus	Prof. Dr. med	Universitätsklinikum Bonn	SP 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	First Name	Title	Institution	Nr	Title
Horger	Marius	Prof. Dr.	Universitätsklinkum Tübingen	SP1	Image-guided multiscale modeling of vascular tumor growth as a systems biology-based tool to predict therapeutic outcome in HCC
Reuss	Matthias	Prof.Dr. Dr.	Stuttgart Research Center Systems Biology		
Perfahl	Holger	Dr.	Stuttgart Research Center Systems Biology		
Witteler-Neul	Beate		Stuttgart Research Center Systems Biology		
Zender	Lars	Prof. Dr.	Universitätsklinikum Tübingen	SP2	In vivo imaging and molecular profiling of treatment responses to anti-angiogenic therapies in murine liver carcinomas of defined genetic origin
Pichler	Bernd	Prof. Dr.	Universität Tübingen		
Kohlbacher	Oliver	Prof. Dr.	University of Tübingen	SP 3	Data integration and management
Daum	Volker	Dr.-Ing.	Chimaera GmbH	SP 4	Using imaging analysis and mining to develop predictive and prognostic models for diagnosis of HCC
Hahn	Dieter	Dr.-Ing.	Chimaera GmbH		
Schmid	Andreas	Dr.	Universität Tübingen	SP 5	
Bezrukov	Ilja		Universität Tübingen		
Malek	Nisar	Prof. Dr.	Universitätsklinikum Tübingen		
Zender	Lars	Prof. Dr.	Universitätsklinikum Tübingen		
Bitzer	Michael	Prof. Dr.	Universitätsklinikum Tübingen		
Pichler	Bernd	Prof. Dr.	Universität Tübingen	SP 6	Management of the Consortium

PANC-STRAT Coordinator: Prof. Dr. Roland Eils					
Coordinator of subproject				**Subproject**	
Name	First Name	Title	Institution	Nr	Title
Hackert	Thilo	Prof. Dr.	University Hospital Heidelberg		
Giese	Nathalia	Dr.	University Hospital Heidelberg		
Strobel	Oliver	PD Dr.	University Hospital Heidelberg		
Weichert	Wilko	Prof. Dr.	University Hospital Heidelberg		
Springfeld	Christoph	Dr.	NCT Heidelberg		Clinical sample collection,
Jäger	Dirk	Prof. Dr.	NCT Heidelberg	SP1	Tissue workup and Histological evaluation
Eils	Roland	Prof. Dr.	DKFZ Heidelberg		
Schlesner	Matthias	Dr.	DKFZ Heidelberg	SP2	High-Through-Put Data Generation and Integrated Data Analysis
Trumpp	Andreas	Prof. Dr.	HI-STEM - Heidelberg Institute for Stem Cell Technology and Experimental Medicine gGmbH		Establishment of patient derived xenograft-models and personalized TIC (tumor-initiating cell) cultures and analysis of the PDAC microenvironment
Sprick	Martin	Dr.	HI-STEM - Heidelberg Institute for Stem Cell Technology and Experimental Medicine gGmbH	SP 3	
Trumpp	Andreas	Prof. Dr.	HI-STEM		
Sprick	Martin	Dr.	HI-STEM		
Eils	Roland	Prof. Dr.	DKFZ Heidelberg		Dynamic Systems Biology
Bauer	Tobias	Dr.	DKFZ Heidelberg	SP 4	Models for Pathway and Drug Discovery
Trumpp	Andreas	Prof. Dr.	HI-STEM		
Sprick	Martin	Dr.	HI-STEM	SP 5	Preclinical Translation
Hackert	Thilo	Prof. Dr.	University Hospital Heidelberg		
Giese	Nathalia	Dr.	University Hospital Heidelberg		
Strobel	Oliver	PD Dr.	University Hospital Heidelberg		
Weichert	Wilko	Prof. Dr.	University Hospital Heidelberg		
Springfeld	Christoph	Dr.	NCT Heidelberg		Clinical Validation and
Jäger	Dirk	Prof. Dr.	NCT Heidelberg	SP 6	Translation
Eils	Roland	Prof. Dr.	DKFZ Heidelberg		
Lawerenz	Christian		DKFZ Heidelberg	SP 7	Integrated Data and Project Management

SMOOSE

Systems-level analysis of modulators of oncogenic signaling

Coordinator: Prof. Dr. Roman Thomas

Coordinator of subproject				**Subproject**	
Name	First Name	Title	Institution	Nr	Title
Thomas	Roman	Prof. Dr.	Universität Köln		
Bosco	Graziella	Dr.	Universität Köln	SP0	Coordinating Office
Fischer	Matthias	Prof. Dr.	Universität Köln		
Schulte	Johannes	Prof. Dr.	Uniklinik Essen	SP1	Genomic characterization and modeling of tumor progression
Peifer	Martin	Dr.	Universität Köln	SP2	Systems-level modeling of cancer genome evolution
Berg	Johannes	Prof. Dr.	Universität Köln	SP3	Systems-level modeling of mutationally activated signaling 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.	Universität Köln	SP5	Identification, validation and exploitation of modulators
Reinhardt	Christian	Prof. Dr.	Universität Köln	SP6	In vivo characterization of oncogenically rewired signaling networks in lung cancer
Büttner	Reinhard	Prof. Dr.	Universität Köln	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.	Universität Köln	SP9	A phase I study for combination of 3rd generation ERGF-inhibitor EGF816 with MEK-inhibitor Trametinib in adult patients with ERFG-mutation positive adenocarcinoma of the lung and acquired EGFRp.T790M resistance mutation

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	First Name	Title	Institution	Nr	Title
Meyer-Hermann	Michael	Prof. Dr.	Helmholtz-Zentrum Braunschweig	SP 1	Mathematisches Modell der Entstehung ektopischer Lymphfollikel im Kontext von Nierentransplantationen
Schönmeyer	Ralf	Dr.	Definiens AG	SP 2	Mining spatial and functional immune cell patterns to develop and clinically validate novel prognostic tissue markers
Hatzikirou	Haralampos	Dr.	Technische Universität Dresden	SP 3	A model of T-cell – epithelial cell interaction in lymphocytic lobulitis at the interface of hereditary breast cancer and adjacent tissue
Feuerhake	Friedrich	Prof. Dr.	Medizinische Hochschule Hannover	SP 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	First Name	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	SP1	Monogenic and oligogenic traits as an entry port to systems medicine
August	Dietrich	-	Universitätsklinikum Freiburg		
Rodriguez	Elke	Dr.	UKSH		
Baurecht	Hansjörg	Dr.	UKSH		
Grimbacher	Bodo	Prof. Dr.	Universitätsklinikum Freiburg		
Kabesch	Michael	Prof. Dr.	Universität Regensburg		
Lieb	Wolfgang	Prof. Dr.	Institut für Epidemiologie	SP2	Kindred cohorts - a tool for systems medicine
Franke	Andre	Prof. Dr.	Universitätsklinikum Schleswig-Holstein	SP3	Host genetics meets microbiome - a systems approach
Rosenstiel	Philip	Prof. Dr.	Universitätsklinikum Schleswig-Holstein		
Baines	John	Prof. Dr.	Universitätsklinikum Schleswig-Holstein		

SysINFLAME A Systems Approach to Chronic Inflammatory Disease Coordinator: Prof. Dr. Philip Rosenstiel, Prof. Dr. Stefan Schreiber					
Coordinator of subproject				**Subproject**	
Name	First Name	Title	Institution	Nr	Title
Rosenstiel	Philip	Prof. Dr.	Universitätsklinikum Schleswig-Holstein		
Häsler	Robert	Prof. Dr.	UKSH, IKMB	SP4	Epigenome /Transcriptome Dynamics
Schreiber	Stefan	Prof. Dr.	Universitätsklinikum Schleswig-Holstein		
Rosenstiel	Philip	Prof. Dr.	Universitätsklinikum Schleswig-Holstein		
Brand	Berenice	Dr.	Universitätsklinikum Schleswig-Holstein	SP5	Drug Response
Radbruch	Andreas	Prof. Dr.	Deutsches Rheuma-Forschungszentrum (DRFZ)		
Grützkau	Andreas	Dr.	Deutsches Rheuma-Forschungszentrum (DRFZ)		
Löhnhardt	Benjamin		Universitätsmedizin Göttingen		
Bauer	Christian		Universitätsmedizin Göttingen		
Baum	Benjamin		Universitätsmedizin Göttingen	SP6	Immune Cell Dynamics
Laudes	Matthias	Prof. Dr.	Klinik für Innere Medizin I		
Schulte	Dominik	Dr.	UKHS, Klinik für Innere Medizin I	SP7	Redefinition of Phenotypes
Ellinghaus	David	Prof. Dr	UKSH, IKMB		
Ellinghaus	Eva	Dr.	IKMB		
Willenborg	Christina	Dr.	UKSH	SP 8	Comorbidities - Genetic redefinition of indications
Hütt	Marc	Prof. Dr.	Jacobs Universität Bremen		
Krawczak	Michael	Prof. Dr.	Institut für Medizinische Informatik und Statistik		
Claussen	Jens Christian	PD Dr.	Jacobs University		
Fretter	Christoph		Jacobs University		Data Analysis and the Promotion of a "System Medicine Dialog"
Wolf	Andreas		UKSH	SP9	
Franke	Andre	Prof. Dr.	IKMB		
Sax	Ulrich	Prof. Dr.	Universitätsmedizin Göttingen		
Krawczak	Michael	Prof. Dr.	Institut für Medizinische Informatik und Statistik		
Radbruch	Andreas	Prof. Dr.	Deutsches Rheuma-Forschungszentrum (DRFZ)		SystemResearch Data Management / Bioinformatics - A Tool for Systems Medicine
Hemmrich-Stanisak	Georg	Dr.	UKSH, IKMB	SP10	

SysMed-Alcoholism Alcohol Addiction: A Systems-Oriented Approach Coordinator: Prof. Dr. Rainer Spanagel					
Coordinator of subproject				**Subproject**	
Name	First Name	Title	Institution	Nr	Title
Spanagel	Rainer	Prof. Dr.	Central Institute of Mental Health	SP 1	Coordination of the Consortium
Nöthen	Markus	Prof. Dr.	Universty of Bonn	SP 2	Central Resource I: Genomics and Epigenomics
Rietschel	Marcella	Prof. Dr.	Central Institute of Mental Health		
Hansson	Anita	Dr.	Central Institute of Mental Health	SP 3	Central Resource II: Transcriptomics platform
Sommer	Wolfgang H.	Prof. Dr.	Central Institute of Mental Health		
Schloss	Patrick	Prof. Dr.	Central Institute of Mental Health		
Schumann	Gunter	Prof. Dr.	King's College London	SP 4	Central Resource III: IMAGEN
Desrivières	Sylvane	Dr.	King's College London		
Matthäus	Franziska	Dr.	BIOMS/IWR	SP 5	Central Resource IV: Animal model of alcohol addiction
Vengeliene	Valentina	Dr.	Central Institute of Mental Health		
Obermeyer	Klaus	Prof. Dr.	Technische Universität Berlin	SP 6	Mathematical Modeling I: Convergent data analysis and statistics
Heinz	Andreas	Prof. Dr. Dr.	Charité		
Schumann	Gunter	Prof. Dr.	King's College London		
Durstewitz	Daniel	Prof. Dr.	Central Institute of Mental Health	SP 7	Mathematical Modeling II: Local neurodynamics and treatment predictions
Noori	Hamid	PD Dr. Dr.	Bernstein Center Heidelberg/Mannheim, Central Institute for Mental Health	SP 8	Mathematical Modelling III: Global Neurotransmitter Dynamics and Target Predictions
Scholz	Henrike	Prof. Dr.	Universität zu Köln	SP 9	Functional Validation I: Gene and molecular analysis
Wurst	Wolfgang	Prof. Dr.	Helmholtz Zentrum Munich		
Heinz	Andreas	Prof. Dr.	Charité	SP10	Functional Validation II: Neuroimaging x genetics
Walter	Henrik	Prof. Dr. Dr.	Charité		
Kiefer	Falk	Prof. Dr.	Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health (CIMH)		

SysMed-Alcoholism Alcohol Addiction: A Systems-Oriented Approach Coordinator: Prof. Dr. Rainer Spanagel					
Coordinator of subproject				**Subproject**	
Name	First Name	Title	Institution	Nr	Title
Köhr	Georg	PD Dr.	Central Institute of Mental Health, Heidelberg University	SP11	Functional network activity and neurotransmitter release
Zimmermann	Ulrich	PD Dr.	University Hospital Carl Gustav Carus	SP12	Platform for Experimental Human Tests
SYSMED-NB Systems Medicine for Neuroblastoma Coordinator: Prof. Dr. Angelika Eggert					
Coordinator of subproject				**Subproject**	
Name	First Name	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		Modeling primary sugar metabolism in neuroblastoma to identify central nodes for therapeutic intervention
Wolf	Jana	Dr.	MDC Berlin	SP B3	
Rahmann	Sven	Prof. Dr.	TU Dortmund		
Fischer	Matthias	Prof. Dr.	Universität zu Köln	SP A1 und SP B2	Targeting the RAS pathway in high-risk neuroblastomas
Schulte	Johannes Hubertus	Prof. Dr.	Universität Duisburg-Essen	SP A2	Mouse modeling and crossspecies analysis to optimize identification and targeting of MYCN co-drivers in NB
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	Translating genomic information to therapeutic targets for neuroblastoma using systematic loss-of-function screening

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	First Name	Title	Institution	Nr	Title
Luber	Birgit	Prof. Dr.	Technische Universität München	SP 1	Systematic molecular and phenotypical characterization of gastric cancer cell lines
Maier	Dieter	Dr.	Biomax Informatics AG	SP 2	Knowledge management and biomarker discovery
Theis	Fabian	Prof. Dr. Dr.	Helmholtz Zentrum München	SP 3	Multi-level analysis of gastric cancer data
Meyer-Hermann	Michael	Prof. Dr.	Helmholtz-Zentrum für Infektionsforschung, Braunschweig	SP 4	Agent-based tumour models to define adjuvant therapy approaches
Walch	Axel	Prof. Dr.	Helmholtz Zentrum München, Institut für Pathologie	SP 5	In situ proteome analysis of gastric cancer
Lordick	Florian	Prof. Dr.	Universitäres Krebszentrum Leipzig (UCCL)	SP 6	Clinical validation of response and resistance factor candidates to targeted therapy in gastric cancer

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
Scholz	Markus	Prof. Dr.	University Leipzig	1.1	Optimisation of adjunctive therapy with haematopoetic groth factors during conventional cytotoxic chemotherapy
Löffler	Markus	Prof. Dr.	University Leipzig		
Scholz	Markus	Prof. Dr.	University Leipzig	1.2	Modelling of leucaemic haematopoesis and its therapy
Löffler	Markus	Prof. Dr.	University Leipzig		
Bornhäuser	Martin	Prof. Dr.	Uniklinik Dresden		
Christian	Thiede	Prof. Dr.	Uniklinik Dresden		
Scholz	Markus	Prof. Dr.	University Leipzig	1.3	Modelling of anaemia treatments with chronic kidney disease
Löffler	Markus	Prof. Dr.	University Leipzig		
Benzing	Thomas	Prof. Dr.	Uniklinik Köln		
von Gersdorff	Gero	Dr.	Uniklinik Köln		
Glauche	Ingmar	Dr.	TU Dresden	2.1	Modelling of treatment kinetics of CML
Röder	Ingo	Prof. Dr.	TU Dresden		
Hochhaus	Andreas	Prof. Dr.	Jena University Hospital		
Rudolph	Karl Lenhard	Prof. Dr.	Leibniz-Institut für Altersforschung		
Glauche	Ingmar	Dr.	TU Dresden	2.2	Modelling of clonal pathogenesis and treatment dynamics in NPM1-positive AMLModelling of anaemia treatments with chronic kidney disease
Röder	Ingo	Prof. Dr.	TU Dresden		
Bornhäuser	Martin	Prof. Dr.	Uniklinik Dresden		
Christian	Thiede	Prof. Dr.	Uniklinik Dresden		
Röder	Ingo	Prof. Dr.	TU Dresden	PM	Project management
Löffler	Markus	Prof. Dr.	University Leipzig	DM	Data management
Röder	Ingo	Prof. Dr.	TU Dresden		
Löffler	Markus	Prof. Dr.	University Leipzig	SWE	Software engineering
Röder	Ingo	Prof. Dr.	TU Dresden		

HER2Low

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

Coordinator: Prof. Dr. Stefan Wiemann

Coordinator of subproject				Subproject	
Name	First Name	Title	Institution	Nr	Title
Wiemann	Stefan	Prof. Dr.	DKFZ Heidelberg	SP 1	Dynamic data of drug response in cell line models of HER2-low breast cancer
Wiemann	Stefan	Prof. Dr.	DKFZ Heidelberg	SP 2	In vitro and in vivo testing of phenotypic model predictions
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

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: Prof. Dr. Dagmar Kulms

Coordinator of subproject				Subproject	
Name	First Name	Title	Institution	Nr	Title
Kulms	Dagmar	Prof. 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		
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		
Jain	Shushant	Dr.	DZNE		
Gasser	Thomas	Prof. Dr.	HIH & DZNE		
Krüger	Rejko	Prof. Dr.	HIH & DZNE		
Klein	Christine	Prof. Dr.	Universität Lübeck		
Ueffing	Marius	Prof. Dr.	Universität Tübingen		
Gloeckner	Christian Johannes	Dr.	Universität Tübingen	TP 4	Validation in cellular models
Wurst	Wolfgang	Prof. Dr.	HelmholtzZentrum München		
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		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	
Löffler	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	Claudio	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
Kühne	Titus	Prof. Dr.	DHZB/Charité		
Knosalla	Christoph	PD Dr.	DHZB		
Nordmeyer	Sarah	Dr.	DHZB	SP 1	Systems Medicine of Heart Failure
Schapranow	Matthieu-P.	Dr.	Hasso-Plattner-Institut	SP 2	Real-Time Analysis of Genome Data using In-Memory Database Technology
Kararigas	Georgios	Dr.	Charité Berlin		
Regitz-Zagrosek	Vera	Prof. Dr.	Charité Berlin		
Robinson	Peter N	Prof. Dr.	Charité Berlin	SP 3	Transcriptome and miRNAome analysis in native and Ang II treated human myocardium
Falcke	Martin	Dr.	MDC für Molekulare Medizin		
Dittmar	Gunnar	Dr.	MDC für Molekulare Medizin	SP 4	Cell physiology modelling and proteomics
Kühne	Titus	Prof. Dr.	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 & University Heidelberg		
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
Löffler	Markus	Prof. Dr.	Universität Leipzig		
Reifenberger	Guido	Prof. Dr.	Universität Düsseldorf		
von Deimling	Andreas	Prof. Dr.	Universität Heidelberg		
Weller	Michael	Prof. Dr.	UniversitätsSpital Zürich	SP 2B	Assessment of crucial pathways in validation cohort

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
Pfister	Stefan	Prof. Dr.	DKFZ		
Liu	Hai-Kun	Dr.	DKFZ		
Gronych	Jan	Dr.	DKFZ	SP 3A	In vivo validation in glioma mouse models
Reifenberger	Guido	Prof. Dr.	Universität Düsseldorf		
Knobbe-Thomsen	Christiane	Dr.	Universität Düsseldorf		
Weller	Michael	Prof. Dr.	UniversitätsSpital Zürich	SP 3B	Experimental modeling of glioma progression and therapy resistance
Lamszus	Katrin	Prof. Dr.	Universitätsklinikum Hamburg-Eppendorf		
Radlwimmer	Bernhard	Dr.	DKFZ	SP 3C	Metabolic adaptations in glioma progression and therapy resistance
Weller	Michael	Prof. Dr.	UniversitätsSpital Zürich		
von Deimling	Andreas	Prof. Dr.	Universität Heidelberg		
Löffler	Markus	Prof. Dr.	Universität Leipzig		
Lichter	Peter	Prof. Dr.	DKFZ		
Reifenberger	Guido	Prof. Dr.	Universität Düsseldorf		
Pfister	Stefan	Prof. Dr.	DKFZ	SP 4	Development of a clinical trial protocol

List of e:Med Junior Research Groups

ComorbSysMed Comorbidity patterns in inflammatory skin diseases: A systems medicine approach using machine learning and omics technologies Coordinator: Dr. Silke Szymczak			
Szymczak	Silke	Dr.	Christian-Albrechts-Universität zu Kiel
DiNGS Entschlüsselung der genetischen Ursachen von Schizophrenie Coordinator: Dr. Michael Ziller			
Ziller	Michael	Dr.	Max-Planck-Institut für Psychiatrie, München
MultiPath A generic multi-layer model for integrating multiple types of pathway knowledge Coordinator: Dr. Frank Kramer			
Kramer	Frank	Dr.	Georg-August-Universität Göttingen
NeuroCon Computational Convergence of Functional and Neurochemical Fingerprints of Psychiatric Drugs Coordinator: PD Dr. Dr. Hamid Noori			
Noori	Hamid	PD Dr. Dr.	Max-Planck Institut für biologische Kybernetik, Tübingen
Bokharaie	Vahid Samadi	Dr.	
Soltanpour	Morteza		
PreNeSt Pre-mapping Networks for Brain Stimulation Coordinator: Dr. Roberto Goya-Maldonado			
Goya-Maldonado	Roberto	Dr.	Georg-August-Universität Göttingen
Quan-T-cell Quantitative T cell immunology to inform immunotherapy and vaccination Coordinator: Dr. Michael Floßdorf			
Floßdorf	Michael	Dr.	Technische Universität München
SYMPATHY Systems medicine approach to establish individualized treatment of lymphoma and leukemia Coordinator: Dr. Sascha Dietrich			
Dietrich	Sascha	Dr.	Ruprecht-Karls-Universität Heidelberg
Rabe	Sophie		Universitätsklinikum Heidelberg
Gaus	Carolin		Universitätsklinikum Heidelberg
SysMedOs Integration of oxidative stress into systems medicine view for obesity and obesity related complications Coordinator: Dr. Maria Fedorova			
Fedorova	Maria	Dr.	Universität Leipzig
Zhixu	Ni		Universität Leipzig
Mike	Lange		Universität Leipzig

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: Prof. 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	Prof. 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: Prof. 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	Prof. 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
Sigurds-son	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. Jan Medenbach

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
Medenbach	Jan	Dr.	Universität Regensburg	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	Prof. 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

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