e:Med
SYSTEMS MEDICINE

e:Med Meeting 2016 on Systems Medicine

October 4 - 6, 2016
Christian-Albrechts-Universität, Kiel

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Welcome Remarks

Dear e:Med colleagues,

It is a great pleasure to cordially welcome you on behalf of the e:Med Project Committee and the local organizers at this year's **e:Med Meeting 2016 on Systems Medicine** at the **Audimax of the Christian-Albrechts University in Kiel,** taking place from **October 4th thru October 6th.** We are looking forward to excellent speakers informing us on their research and the latest developments in systems medicine within e:Med and beyond.

The annual e:Med meeting is by now established as a central platform for the interdisciplinary exchange within and outside the e:Med community. Experts, advanced and junior scientists gather to share their latest findings in keynote lectures, short talks or poster flash talks, poster sessions or during our delightful evening events. An additional highlight this year will be the panel discussion on "What will the medicine of the future look like?".

We decided to center this year's program on the cross-topic issues disease manifestation, heterogeneity of disease and therapy response prediction. In addition, a special focus will be on infectious, inflammatory and neuropsychiatric disorders. The joined activities will be presented in the European integration sessions and sessions of the e:Med project groups. As modern life sciences continue to raise complex ethical, legal and social aspects (ELSA), we also included a dedicated "ELSA of systems medicine" session in the program. Moreover, recent technological developments will be on display in talks and an industrial exhibition.

We are convinced that the meeting will inspire stimulating discussions and provides a great opportunity for establishing new collaborations and multifaceted networking activities in systems medicine. You are kindly invited to exploit and enjoy the multidisciplinary research presentations from e:Med and our distinguished guest speakers as much as possible to think outside the box of your own work!

A very warm welcome to all of you here in Kiel!

Professor Dr. Tanja Zeller

PD Dr. Karsten Rippe

Speakers of the e:Med project committee

Scientific Program Committee

Prof. Dr. Jeanette Erdmann
Institute for Integrative and Experimental Genomics, University Lübeck

Prof. Dr. Friedrich Feuerhake
Institute for Pathology, Hannover Medical School

Prof. Dr. Titus Kühne
Deutsches Herzzentrum Berlin, Charité - Universitätsmedizin Berlin

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

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

Prof. Dr. Philip Rosenstiel
Institute of Clinical Molecular Biology (IKMB), Kiel, University Hospital Schleswig-Holstein

Prof. Dr. Rainer Spanagel
Institute for Psychopharmacology, ZI Mannheim

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

Members of the e:Med Project Committee

Prof. Dr. Jeanette Erdmann, University of Lübeck

Prof. Dr. Friedrich Feuerhake, Hannover Medical School

Prof. Dr. Hartmut Goldschmidt, University Hospital Heidelberg

Dr. Roberto Goya-Maldonado, Georg August University Göttingen

Prof. Dr. David Hassel, University Hospital Heidelberg

Prof. Dr. Steffen Just, University Hospital Ulm

Dr. Frank Kramer, Georg August University Göttingen

Prof. Dr. Titus Kühne, Deutsches Herzzentrum Berlin

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

Prof. Dr. Markus Nöthen, University of Bonn

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

Prof. Dr. Ingo Röder, Technische Universität Dresden

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

Dr. Martin Sos, University Hospital of Cologne

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

Prof. Dr. Rainer Spang, Institute of Functional Genomics, 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

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Local organisation

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Program

Tuesday, October 4, 2016

01:00 - 01:30 pm	**Registration & Welcome Coffee**
01:30 - 01:45 pm	**Welcome Address** **Tanja Zeller,** Spokesperson e:Med Project Committee **Johannes Mohr**, Bundesministerium für Bildung und Forschung **Ulrich Stephani**, Dekan der medizinischen Fakultät der CAU Kiel
01:45 - 03:15 pm	**Cross-topic Issues I - Disease Manifestation**
	Chair: Tanja Zeller, Dagmar Kulms
01:45 - 02:30 pm	**Trey Ideker**, UC San Diego *Siri of the Cell – Intelligent agents for systems medicine constructed using systems data*
02:30 - 02:45 pm	**Julia Fitzgerald**, Hertie Institute *A knockout PINK1 model of Parkinson's disease in iPSC-derived neurons*
02:45 - 03:00 pm	**Wolfgang Lieb**, CAU Kiel *IBD kindred cohort: A tool for systems medicine*
03:00 - 03:15 pm	**Julio Vera**, Erlangen University Hospital *A platform for the network analysis of expression data from human inflammatory macrophages in bacterial lung infections*
03:15 - 03:45 pm	**Coffee Break**
03:45 - 05:45 pm	**Specific Diseases I - Infection & Inflammation**
	Chair: Philip Rosenstiel, Friedrich Feuerhake
03:45 - 04:30 pm	**Mamoru Watanabe**, Tokyo Medical and Dental University *Intestinal Epithelial Stem Cells for the Treatment of Colitis*
04:30 - 05:15 pm	**John M. Burke**, Applied BioMath, Lincoln, MA *Quantitative modeling and simulation approaches: providing deep biological hypotheses and driving critical decisions from research through clinical trials for inflammation and immunology*
05:15 - 05:30 pm	**Arturo Blázquez Navarro**, Berlin-Brandenburg Center for Regenerative Therapies *Differential immune response against structural and regulatory BK virus antigens explains kinetics of BK viremia in kidney transplant patients*
05:30 - 05:45 pm	**Raheleh Sheibani**, IKMB Kiel *Uncoupling of Mucosal Gene Regulation, Splicing and Microbiota Signatures in Inflammatory Bowel Disease*
05:45 - 06:15 pm	**Coffee Break**
06:15 - 07:15 pm	**Joint Activities – Panel Discussion** ***Wohin bewegt sich die Medizin der Zukunft?***
	Moderation: **Burkhard Plemper**, Journalist, Gesundheits- und Sozialpolitik
	Ulrike Holtkamp, Patientenorganisation Deutsche Leukämie-& Lymphom-Hilfe e.V. **Stefan Schreiber,** UKSH Kiel **Alena Buyx,** Professor of Biomedical Ethics, CAU Kiel **Lore Gruenbaum,** Applied BioMath, Lincoln, MA **Ernst Theodor Rietschel,** Gründungsdirektor des Berliner Instituts für Gesundheitsforschung, EU-Beauftragter acatech Präsidium, ehem.Präsident der Leipniz Gesellschaft
07:15 - 10:00 pm	**Get together with Wine & Snacks at the venue**

Wednesday, October 5, 2016

08:30 - 09:00 am	**Welcome Coffee**
09:00 - 10:30 am	**Cross-topic Issues II - Heterogeneity of Disease** **Chair: Maria Fedorova, Stefan Wiemann**
09:00 - 09:45 am	**Elaine Holmes**, Imperial College London
09:45 - 10:00 am	**Inn Chung**, DKFZ Heidelberg *Classification of pediatric glioblastoma according to their telomere maintenance features*
10:00 - 10:15 am	**Andre Franke**, Universitätsklinikum Schleswig-Holstein, Kiel *Genome-wide host-microbiota association analysis of 1,812 individuals identifies vitamin D receptor genetic variation and other host factors shaping the gut microbiota*
10:15- 10:30 am	**Jens Christian Claussen**, Jacobs University Bremen *Abundance vector shifts under Boolean operations reveal systematic interactions of low-abundance species in the human gut microbiome*
10:30 - 11:00 am	**Coffee Break**
11:00 - 11:30 am **11:30 - 12:30 pm**	**Joint Activities - Poster Flash Talks I** **Joint Activities - Poster Exposition I**
12:30 - 02:00 pm	**Lunch Break - Company Lunch Talks**
01:00 - 01:30 pm	**Martin Heine**, NuGEN *RNA-Seq and DNA-Seq from Picogram Inputs*
01:30 - 02:00 pm	**Dirk Bartels**, Illumina **Per Hoffmann**, Life & Brain *3rd Generation Arrays: New Global Screening Array (GSA) and New Methylation EPIC Array*
02:00 - 04:00 pm	**Specific Diseases II - Neuropsychiatric Disorders** **Chair: Markus Nöthen, Rainer Spanagel**
02:00 - 02:45 pm	**Wolfgang H. Sommer**, ZI Mannheim *A systems medicine approach for better understanding of alcohol addiction*
02:45 - 03:00 pm	**Anna Maaser**, University of Bonn *Exome sequencing of European families densely affected with bipolar disorder reveals rare variants in neuronal genes contributing to disease etiology*
03:00 - 03:15 pm	**Andreas Forstner**, University of Bonn *Identification of shared risk loci and pathways for bipolar disorder and schizophrenia*
03:15 - 03:30 pm	**Theo Kraus**, Ludwig-Maximilians-Universität *Cell-type specific Analysis of Epigenome-Wide Methylation Differences in Schizophrenia Brains*
03:30 - 03:45 pm	**Roberto Goya-Maldonado,** University Medical Center Göttingen *Intranasal oxytocin selectively modulates large-scale brain networks*
03:45 - 04:00 pm	**Fabian Theis, Helmholtz Zentrum München** *DeepWAS: Directly integrating regulatory information into GWAS using deep learning identifies risk factors for major depressive disorder*

Wednesday, October 5, 2016

04:00 - 04:30 pm	**Coffee Break**
04:30 - 05:40 pm	**Joint Activities – ELSA of Systems Medicine** **Chair: Matthias von Witsch (DLR-PT)**
04:30 - 05:00 pm	**Wolfgang van den Daele**, Wissenschaftszentrum für Sozialforschung, Berlin *Keynote - Medical Innovation: Handle ELSA with Care!*
05:00 - 05:20 pm	**Pauline Mantell**, Universität zu Köln *Acceptance of systems medicine by people at risk for mental disorders – Preliminary results of a qualitative study*
05:20 - 05:40 pm	**Martin Langanke**, Universität Greifswald *Translation of Systems Medicine into Clinical Routine Care – Results from an Online Survey*
05:40 - 06:10 pm	**Joint Activities - Poster Flash Talks II**
06:10 - 07:00 pm	**Joint Activities - Poster Session II**
07:00 - 11:00 pm	**Shuttle to Pier** **Dinner on paddle steamer ship along the fjords of Kiel**

Thursday, October 6, 2016

08:30 - 09:00 am	**Welcome Coffee**
09:00 - 10:30 am	**Joint Activities - e:Med Project Groups**
09:00 - 09:25 am	**Matthias Gietzelt,** Universitätsklinikum Heidelberg *PG Informatics & Modeling*
09:25 - 09:50 am	**Ulrich Sax**, Universitätsmedizin Göttingen *PG Data Security & Ethics*
09:50 - 10:10 am	**Julia Mannheim,** University of Tübingen *PG Image Processing*
10:10 - 10:30 am	**Karsten Rippe**, DKFZ Heidelberg *PG Epigenetics & Sequencing*
10:30 - 11:00 am	**Coffee Break**
11:00 - 12:30 pm	**Joint Activities - European Integration** **Chair: Jeanette Erdmann, Ingo Röder**
11:00 - 11:40 am	**Arnd Hoeveler,** European Commission, Brussels *The role of systems medicine from EC perspective*
11:40 - 12:10 pm	**Olaf Wolkenhauer**, University Roststock *Are we seeing the beginning, or the end of Systems Medicine?*
12:10 - 12:30 pm	**Mikael Benson**, Linköping University *Clinical perspective of opportunities and challenges related to multidisciplinary collaborations in systems medicine*
12:30 - 02:00 pm	**Lunch Break - Company Lunch Talk**
01:00 - 01:30 pm	**Anika Joecker**, QIAGEN Bioinformatics *Sample-to-Insight NGS Solutions for Liquid Biopsy, hereditary disease and cancer clinical testing, microbiome and RNA-sequencing Analysis and Interpretation*
02:00 - 03:30 pm	**Cross-topic Issues III - Therapy Response Prediction** **Chair: Karsten Rippe, Frank Kramer**
02:00 - 02:45 pm	**Andrea Califano**, Columbia University, NY *Systematic elucidation and pharmacological targeting of tumor checkpoints: a new take on precision cancer medicine*
02:45 - 03:00 pm	**Harry Freitas da Cruz**, Hasso-Plattner Institut Potsdam *ICT Platform for to Enable Consortium work for Systems Medicine of Heart Failure*
03:00 - 03:15 pm	**Patricia Wenk**, Werner Siemens Imaging Center, Tübingen *Bridging PET/MR Imaging and Metabolomics: Sorafenib Changes the Metabolic Profile in HCC Tumor Mouse Model*
03:15 - 03:30 pm	**Agustin Rodriguez-Gonzales**, DKFZ Heidelberg *Precision pharmacology towards the optimal treatment in lung cancer associated anemia*
03:30 - 03:45 pm	**e:Med Poster Award Ceremony** **Closing Remarks** **Karsten Rippe,** Spokesperson e:Med Project Committee
03:45 - 04:15 pm	**Coffee & Snacks**

Directly following:
International Symposium on Systems Medicine of Chronic Inflammatory Disorders
Location: ZMB, Kiel (10 minutes walking distance)
http://www.ikmb.uni-kiel.de/sysinflame-emed-symposium-6-7-october-2016-kiel-germany

Speakers

Tuesday, October 4, 2016 - Cross-topic Issues I - Disease Manifestation

01:45 - 02:30 pm

Keynote - Siri of the Cell – Intelligent agents for systems medicine constructed using systems data
Trey Ideker

Dr. Ideker is a Professor of Medicine at UC San Diego. He is the Director of the San Diego Center for Systems Biology and the Director of the National Resource for Network Biology, as well as being Adjunct Professor of Computer Science and Bioengineering and Member of the Moores UCSD Cancer Center.
Ideker received Bachelor's and Master's degrees from MIT in Electrical Engineering and Computer Science and his Ph.D. from the University of Washington in Molecular Biology under the supervision of Dr. Leroy Hood.
Dr. Ideker is a pioneer in using genome-scale measurements to construct network models of cellular processes and disease. He has founded influential bioinformatic tools including Cytoscape, a popular network analysis platform which has been cited >12,000 times. Ideker serves on the Editorial Boards for Cell, Cell Reports, Nature Scientific Data, EMBO Molecular Systems Biology, and PLoS Computational Biology and is a Fellow of AAAS and AIMBE. He was named one of the Top 10 Innovators of 2006 by Technology Review magazine and was the recipient of the 2009 Overton Prize from the International Society for Computational Biology.

02:30 - 02:45 pm

A knockout PINK1 model of Parkinson's disease in iPSC-derived neurons
Julia Fitzgerald

Julia Fitzgerald received her PhD in mitochondrial biochemistry from NTU, Nottingham and then specialized in the molecular mechanisms of Parkinson's disease at UCL, London. She is now leading several projects on the biological mechanisms underlying neurodegeneration at The Hertie Institute for Clinical Brain Research in Tübingen. She is currently working on mitochondrial and cellular quality control systems in neurons and her main interests lie in mitochondrial physiology and the endosomal-lysosomal system. She has previously worked on mitochondrial proteins that are associated with dopaminergic neuronal death, such as the HtrA2/Omi, Monoamine Oxidase and PINK1. Her approach is to combine several model systems such as patient-derived cells and iPSC-derived neurons with biochemical, genetic and imaging techniques. She is involved in several collaborative projects and is a scientist that is enthusiastic about inter-disciplinary and clinic-bridged research.

Tuesday, October 4, 2016 - Cross-topic Issues I - Disease Manifestation

02:45 - 03:00 pm

IBD kindred cohort: A tool for systems medicine
Wolfgang Lieb

Wolfgang Lieb is Director of the Institute of Epidemiology and Head of the PopGen Biobank at Kiel University and the University Hospital Schleswig-Holstein, Campus Kiel. He combines population-based and clinical epidemiological approaches in order to investigate the development and determinants of inflammatory disease conditions, such as inflammatory bowel disease (IBD), and of common cardiovascular diseases. He is principle investigator of the Kiel IBD kindred cohort, a family-based prospective study, including affected and unaffected family members of patients with IBD. This study aims to identify molecular signatures as well as environmental factors that predict the clinical onset of IBD or that correlate with preclincal stages of IBD.

03:00 - 03:15 pm

A platform for the network analysis of expression data from human inflammatory macrophages in bacterial lung infections
Julio Vera

Julio Vera-Gonzalez studied applied physics. He did his PhD on mathematical modelling of biochemical pathways at the University of La Laguna, Spain (2000-2005). He was postdoctoral researcher at the University of Rostock, Germany, in the first EU project on systems biology of cancer cell signalling (EU-FP6-COSBICS, 2005-2008), and research group leader in systems biology of cancer and aging (2008-2013). From May 2013, he is associated professor in systems tumour immunology at the Department of Dermatology, Erlangen University Hospital and FAU Erlangen-Nürnberg, Germany. His expertise is in analysis of signaling, gene regulatory and miRNA networks in biomedicine, with a focus in immunology and tumor immunology. To this end, his team combines techniques from bioinformatics and computational biology, high through put data analysis, model simulation and analysis and method from multicriteria decision. He currently participates in the BMBF funded CAPSyS-e:Med and MelEVIR-e:Bio projects.

Tuesday, October 4, 2016 - Specific Diseases I - Infection & Inflammation

03:45 - 04:30 pm

Keynote I - Intestinal Epithelial Stem Cells for the Treatment of Colitis
Mamoru Watanabe

Dr. Watanabe is the Vice President of Tokyo Medical and Dental University, the Professor and Chairman in the Department of Gastroenterology and Hepatology and the Director in the Advanced Clinical Center for IBD. He has been working on IBD for years and published over 350 articles in journals including Nature, Nature Medicine, Cell Stem Cell and Immunity. He had been serving as a Chairman of the nation-wide, government-organized Japanese IBD research committee for 7 years. He is the President of AOCC, a member of the IOIBD and ECCO. He is now the Vice President of the Japanese Society of Gastroenterology, and the President of the Japanese Society of IBD, that of Mucosal Immunology and that of Small Intestinal Disease. He had been an Editor-in-chief of Journal of Gastroenterology for 6 years. He is now an Editor-in-chief of Journal of Gastroenterology and Hepatology. He received the Marshall and Warren Lectureship Award in Gastro 2013 APDW/WCOG. His major research interests are in the cellular and molecular biological aspects of IBD, regeneration medicine by intestinal epithelial stem cells, and mucosal immunology.

04:30 - 05:15 pm

Keynote II - Quantitative modeling and simulation approaches: providing deep biological hypotheses and driving critical decisions from research through clinical trials for inflammation and immunology
John M Burke

Dr. Burke's BS and MS are in Applied Mathematics from the University of Massachusetts, Lowell, in 1993 and 1995, respectively. His PhD degree is in Applied Mathematics from Arizona State University in 2003. His research interests include singularly and randomly perturbed differential equations, bifurcation theory, and applying dynamical systems theory to study and understand how cells and tissues make decisions in humans, and human disease.Prior to co-founding Applied BioMath, Dr. Burke joined Boehringer Ingelheim in 2008 as Associate Director, Head of Systems Biology. In 2011, he was promoted to Senior Principal Scientist. At Boehringer Ingelheim, he started, developed and managed the Global Systems Biology and Pharmacoloy group, portfolio, and strategy. The group was responsible for applying systems techniques to the drug discovery process across all Research sites, and supporting Development and Medicine. Prior to Boehringer Ingelheim, Dr. Burke was at Merrimack Pharmaceuticals, Co-Scientific Director of the Cell Decision Processes Center, Systems Biology Department, HMS, and was a Sr. Postdoctoral Fellow in Douglas A. Lauffenburger's lab, Biological Engineering Department, MIT. While at MIT and HMS, Dr. Burke provided consulting or advising for various companies, including AstraZeneca, Pfizer, Momenta, Matlab, and RES Group. Presently he is an on the advisory boards for the MIT "Human Physiome on a Chip" MIT-DARPA Program, and the Mathematics Department at the University of Massachusetts, Lowell. Presently he is developing a systems course for Harvard Medical School that he will be teaching in 2017.

Tuesday, October 4, 2016 - Specific Diseases I - Infection & Inflammation

05:15 - 05:30 pm

Differential immune response against structural and regulatory BK virus antigens explains kinetics of BK viremia in kidney transplant patients
Arturo Blázquez Navarro

Arturo Blázquez Navarro holds a MSc in Biotechnology (Licenciatura en Biotecnología) from the Universitat Politècnica de València. After a Marie Curie Fellowship, he is currently pursuing his doctorate at the Humboldt-Universität zu Berlin. He works under the supervision of Prof. Dr. Nina Babel at the Berlin-Brandenburg Centrum für Regenerative Therapien on the topic of mathematical modelling and statistical analysis of the BK virus infection and the immune response against it, as a part of the e:Kid consortium. e:Kid as a collaborative project which has as its main objective the biomarker guided personalisation of the immunosuppressive therapies after kidney transplantation.

05:30 - 05:45 pm

Uncoupling of Mucosal Gene Regulation, Splicing and Microbiota Signatures in Inflammatory Bowel Disease
Raheleh Sheibani

Raheleh Sheibani tezerji is a junior scientist at the Institute of Clinical Molecular Biology (IKMB) in Kiel. She obtained her PhD from Computational Systems Biology (CUBE) division at Vienna University on host-endophyte interaction and communication. Her graduate research resulted in investigating the genetic attributes that could explain the phenotypic differences between closely related bacteria with different lifestyle regarding their interaction with their host. She is eager to explore the time course of the transcriptional response to various treatments in inflammatory bowel disease (IBD). Especially the crosstalk between chronic inflammatory disease course and transcriptional signatures from patients with IBD is the focus of her current project.

Top Thema

06:15 - 07:15 pm Wohin bewegt sich die Medizin der Zukunft?

Moderation:
Burkhard Plemper

Burkhard Plemper studierte Soziologie, Psychologie und Pädagogik an der Universität Hamburg, Schwerpunkt „Abweichendes Verhalten und Soziale Kontrolle“, Abschluss Dipl. Soziologe, erforschte in einem praxisorientierten Projekt der Hamburger Justiz richterliche Entscheidungen zur Untersuchungshaft, war an der Universität Hamburg an der Evaluation des Opferentschädigungsgesetzes beteiligt, hat mit Gefangenen im Strafvollzug gearbeitet. Er lehrt Soziologie an einer Hochschule für soziale Arbeit, realisiert Dokumentationen über soziale Probleme – z. B. Demenz - für die Fernsehsender der ARD und produziert Filme zur Patientensicherheit für Europäische Kliniken. Er moderiert Diskussionen im Radio – auf NDR-info – und auf Kongressen.

Ulrike Holtkamp

Dr. med. Ulrike Holtkamp ist stellvertretende Vorsitzende des Vorstandes der Stiftung Deutsche Leukämie- & Lymphom-Hilfe. Frau Holtkamp hat Humanmedizin in Köln studiert und dort auch promoviert. Ihre weitere ärztliche Ausbildung hat sie am Institut für Humangenetik der Universität Bonn absolviert und sich zudem im Bereich Gesundheitsmanagement und Psychosozialer Onkologie fortgebildet. Bereits seit 1996 ist sie als Patientenbeistand der Deutschen Leukämie- & Lymphom-Hilfe e.V. tätig, wo sie seit 2010 auch als Geschäftsführerin für den Bereich Medizin fungiert. Darüber hinaus ist sie als Sprecherin der Patientenvertretung des Unterausschuss Methodenbewertung der und als themenbezogene Patientenvertreterin im Unterausschuss Arzneimittel des G-BA (Gemeinsamer Bundesausschuss) aktiv.
Frau Holtkamp setzt sich für die bessere Versorgung von Menschen mit hämatoonkologischen Systemerkrankungen ein, dabei engagiert sie sich bspw. für die gesetzliche Regulierung von Medikamentenlieferengpässen, besucht Diskussionsrunden und ist an der Erarbeitung von Leitlinien als Autorin beteiligt.

Top Thema

Stefan Schreiber

Professor Schreiber ist Direktor der Klinik für Innere Medizin I mit den Schwerpunkten Gastroenterologie, Hepatologie, Pneumologie, Rheumatologie, Infektiologie, Endokrinologie, Adipositas, Ernährungs- und Altersmedizin am UKS-H, Campus Kiel sowie Direktor des Instituts für Klinische Molekularbiologie (IKMB) der Christian-Albrechts-Universität zu Kiel (CAU). Er ist Sprecher des Exzellenzclusters Schleswig-Holstein, „Inflammation at Interfaces“, Aufsichtsratsmitglied des Frankfurter Innovationszentrum Biotechnologie und Mitglied verschiedener „Scientific Advisory Boards“ (z.B. österreichisches Genomprojekt, biotechnologisch ausgerichtete Firmen in Deutschland und Nordamerika, DCCV) und zahlreicher Gesellschaften (z.B. American Gastroenterological Association, European Society of Clinical Investigation, Deutsche Gesellschaft für Innere Medizin etc.). Prof. Schreiber ist im Editorial Board bzw. Editor verschiedener Fachzeitschriften (Gastroenterology, Journal of Molecular Medicine, International Journal of Colorectal Disease, Inflammatory Bowel Disease, Public Library of Science-Medicine). 1998 erhielt er den Martin-Gülzow-Preis der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten, 1996 den Frerichs Preis der Deutschen Gesellschaft für Innere Medizin. Professor Schreiber ist Autor von mehr als 800 Originalarbeiten (Nature Genetics, Nature Medicine, New England Journal of Medicine, Nature Biotechnology, The Lancet, PNAS, PLOS Medicine, Journal of Immunology und Gastroenterology etc.)

Alena Buyx

Professor Dr. med. Alena Buyx, M.A. phil., FRSA, ist Professorin für Medizinische Ethik am Institut für Experimentelle Medizin der CAU Kiel. Nach Studien der Medizin, Philosophie und Soziologie in Münster, London und York sowie Staatsexammen, Magister und Promotion im Jahr 2005 war sie wissenschaftliche Mitarbeiterin am Institut für Ethik, Geschichte und Theorie der Medizin an der WWU Münster. Von dort ging sie für ein Forschungsjahr an das Harvard Program in Ethics and Health der Harvard Medical School. 2009 bis 2012 war sie stellvertretende Direktorin des englischen Ethikrats in London, bevor sie mit einer Emmy Noether-Gruppe an die WWU Münster zurück kehrte, wo sie sich 2013 in Ethik, Geschichte und Theorie der Medizin habilitierte. 2014 erfolgte der Ruf nach Kiel. Alena Buyx bearbeitet die gesamte Breite der biomedizinischen Ethik und Theorie. Sie publiziert hochrangig zu ihren Forschungsthemen in verschiedenen Drittmittelprojekten, organisiert klinisch-ethische Beratung, berät große Forschungskonsortien und hält zahlreiche öffentliche Vorträge. Sie ist u.a. Mitglied des Deutschen Ethikrats.

Top Thema

Lore Gruenbaum

Lore Grünbaum ist Geschäftsführerin des Bereichs Biologie und Pharmakologie bei Applied Biomath. Applied Biomath hat sich auf die Modellierung und Analyse quantitativer System-Pharmakologie zur Optimierung der Arzneimittel-Forschung und -Entwicklung spezialisiert. Dr. Grünbaum ist Biochemikerin und Molekularbiologin mit 15-jähriger Erfahrung im Bereich der Arzneimittelforschung und klinischer Entwicklung, sowie in der Diagnostik und in der personalisierten Medizin. Zuvor war sie Abteilungsleiterin für den Bereich Biomarker Entwicklung für Infektionskrankheiten bei Roche. Dort war sie für die Identifizierung von therapeutischen Ansatzpunkten und Biomarkern verantwortlich, leitete präklinische und klinische Biomarker-Studien sowie experimentelle Studien. Dr. Grünbaum hat an der Freien Universität (Berlin) in Biochemie mit „Summa cum Laude“ promoviert. Ihren Post-Doc hat sie an der Yale Universität im Bereich der Neurowissenschaften gemacht. Vor ihrer Tätigkeit bei Roche hat Dr. Grünbaum neun Jahre bei Boehringer Ingelheim Pharmaceuticals, CT als leitende Forscherin gearbeitet. Dort hat sie mehrere präklinische Methoden entwickelt, mit Fokus auf zellulärer- und in vivo- Bildgebung, Toxikologie und High-Content- Biologie, um Signalwegsanalysen zu ermöglichen und den Wirkmechanismus von Medikamenten besser zu verstehen.

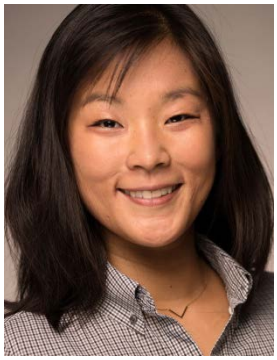
Ernst Theodor Rietschel

Prof. Dr. Dr. h.c. mult. Ernst Theodor Rietschel, geboren am 21.05.1941, studierte Chemie an den Universitäten von München und Freiburg. Nach seiner Promotion am Max-Planck-Institut für Immunbiologie in Freiburg im Jahre 1973 und der 1978 erfolgten Habilitation in Biochemie an der Universität Freiburg wurde er im Jahre 1980 C4-Professur für Immunchemie an der Universität Lübeck und Direktor am Forschungszentrum Borstel, Leibniz-Zentrum für Medizin und Biowissenschaften in Borstel. Die Schwerpunkte seiner wissenschaftlichen Arbeiten lagen auf dem Gebiet der Immunbiologie und Strukturchemie der Endotoxine sowie im Bereich der bakteriellen Sepsis. Zwischen 2005 und 2010 war Ernst Rietschel Präsident der Leibniz-Gemeinschaft, von 2013 bis 2015 leitete er als Vorstandsvorsitzender das neu gegründete Berliner Institut für Gesundheitsforschung/Berlin Institute of Health (BIH).

Wednesday, October 5, 2016 – Cross-topic Issues II - Heterogeneity of Disease

09:00 - 09:45 am **Keynote**
Elaine Holmes

09:45 - 10:00 am **Classification of pediatric glioblastoma according to their telomere maintenance features**
Inn Chung



Inn Chung performed her PhD work in the group of Karsten Rippe at the German Cancer Research Center (DKFZ, Heidelberg). Here she started her work on the cellular processes that allow cancer cells to maintain their chromosomal ends (telomeres), a prerequisite for their unlimited proliferation. In particular, she investigated the structure and function of specific nuclear bodies that are involved in the 'Alternative Lengthening of Telomeres' (ALT) mechanism that is active in 10-15% of cancers. She then joined Xiaolan Zhao's laboratory at Memorial Sloan Kettering Cancer Center, NY, USA, to study the role of posttranslational modifications by SUMO in the DNA double-strand break response. In 2015, Dr. Chung returned to the Rippe group to take part in the CancerTelSys consortium, which works on the identification and characterization of telomere maintenance networks in tumors in order to exploit them for diagnosis, patient stratification, and the development of targeted therapies.

10:00 - 10:15 am **Genome-wide host-microbiota association analysis of 1,812 individuals identifies vitamin D receptor genetic variation and other host factors shaping the gut microbiota**
Andre Franke

I received my PhD 2006 in Molecular Cell Biology, became W1 professor in 2008, received the W2 Peter Hans Hofschneider endowment professorship in 2011 and became W3 Professor for Molecular Medicine at Kiel University in 2016. Since 2011 I am director of the Institute of Clinical Molecular Biology where I coordinate the different Core Facilities (Biobank, Genotyping, Sequencing, Bioinformatics).
My main scientific interests are the development and establishment of novel high-throughput technologies, the inherent bioinformatic integration and application of both to identify genetic and non-genetic causes of chronic inflammatory diseases such as Crohn's disease, ulcerative colitis, psoriasis, and primary sclerosing cholangitis. Having worked on genome-wide association studies for the last years, my research agenda currently focuses on targeted enrichment strategies (e.g. for the HLA/MHC), whole-exome sequencing of early-onset patients, gene-environment interaction analyses including gut microbiome studies and clinical diagnostics.

Wednesday, October 5, 2016 – Cross-topic Issues II - Heterogeneity of Disease

10:15- 10:30 am

Abundance vector shifts under Boolean operations reveal systematic interactions of low-abundance species in the human gut microbiome
Jens Christian Claussen

Jens Christian Claussen received a PhD (1999), habilitation and venia legendi (2005) in Theoretical Physics at Christian-Albrecht-University Kiel from where he moved 2008 to the University of Luebeck. Since 2013, he is Coordinator of the Computational Life Science (MSc) program at Jacobs University Bremen and lecturing courses in Theoretical Biology, Systems Biology, Dynamical Systems, Networks and Complex Systems. His research aims at theoretical and computational understanding of dynamical phenomena in biological systems, namely brain oscillations, pattern formation, RNA interference, control of biological systems, diversity and dynamics of populations with mutualistic interactions, and evolutionary dynamics. He (co)authors about 50 refereed publications with 700+ citations and has supervised about 20 students on BSc, MSc, Diploma and PhD level, received grants from DFG/SFB and BMBF/Bernstein/NIH and is currently chairing a Division at the German Physical Society.

Wednesday, October 5, 2016 – Specific Diseases II - Neuropsychiatric Disorders

02:00 - 02:45 pm

Keynote - A systems medicine approach for better understanding of alcohol addiction
Wolfgang H. Sommer

Studies in medicine at University of Greifswald (1981-1987), doctoral degree in molecular virology at Humboldt University, Berlin (1992). Board certification in psychiatry and appointed to associate professor in experimental psychiatry at the Karolinska Institute, Stockholm, Sweden, in 2001. Unit director Molecular Pathophysiology at NIAAA/NIH, Bethesda, Maryland, USA (2004-2008). Since 2008 deputy scientific director of the Institute for Psychopharmacology, Central Institute of Mental Health, Mannheim Germany. Venia legendi at University of Heidelberg since 2011. Research interests include basic and translational studies of the neurobiological mechanisms underlying addictive behaviors. Editorial board member of Addiction Biology and of Alcoholism: Clinical and Experimental Research. Coordinator of the Horizon2020 project SyBil-AA: Systems Biology of Alcohol Addiction.

Wednesday, October 5, 2016 – Specific Diseases II - Neuropsychiatric Disorders

02:45 - 03:00 pm

Exome sequencing of European families densely affected with bipolar disorder reveals rare variants in neuronal genes contributing to disease etiology
Anna Maaser

Anna Maaser was born in 1986 and studied Biology at the University of Bonn. At the Institute of Cell Biology she performed her diploma thesis entitled “Influence of bacterial factors on the *in vitro* fusion of phagosomes with lysosomes”. She investigated the impact of bacterial factors on phagocytic organelles isolated from macrophages in a cell-free model and received her diploma in 2013. She started her PhD in July 2014 at the Institute of Human Genetics of the University of Bonn. Her work is situated in the research area of neuropsychiatric diseases in the working group “Affective Disorders” which is led by Prof. Markus Nöthen and Dr. Andreas Forstner. The main focus of her work is the definition of a high-confidence set of risk genes by performing whole exome sequencing studies in multiply affected families with bipolar disorder and subsequent bioinformatics analyses. She is responsible for the execution of the experimental work as well as for the analysis and validation of the generated exome sequencing data. In addition, she is also involved in related research projects.

03:00 - 03:15 pm

Identification of shared risk loci and pathways for bipolar disorder and schizophrenia
Andreas Forstner

Dr. Andreas Forstner was born in 1985, and studied Medicine at the University of Bonn in Germany. From October 2012 to May 2016, he was an assistant doctor and postdoctoral fellow at the Institute of Human Genetics, University Hospital of Bonn. Since June 2016, he has worked as an assistant doctor at the Department of Psychiatry and in the Human Genomics Research Group of the Department of Biomedicine, University of Basel, Switzerland. His area of research is the molecular analysis of neuropsychiatric disease. Together with Prof. Markus Nöthen, he leads the “Affective Disorders” research group at the Institute of Human Genetics in Bonn.During his undergraduate medical studies in Bonn, Andreas Forstner performed the experimental work for his medical thesis at the Institute of Human Genetics. Here, he applied a molecular-genetic approach to investigate the role of a microRNA (miR-185) in the development of schizophrenia. Andreas Forstner is a recipient of scholarships from the German National Academic Foundation, the BONFOR program of the Medical Faculty of the University of Bonn, and the German Society of Human Genetics.

Wednesday, October 5, 2016 – Specific Diseases II - Neuropsychiatric Disorders

03:15 - 03:30 pm **Cell-type specific Analysis of Epigenome-Wide Methylation Differences in Schizophrenia Brains**
Theo Kraus

03:30 - 03:45 pm **Intranasal oxytocin selectively modulates large-scale brain networks**
Roberto Goya-Maldonado

Dr. Roberto Goya-Maldonado was born in 1976 in Porto Alegre, Brazil, where he later studied and practiced Medicine at the Federal University of Rio Grande do Sul. He became a Psychiatrist in 2005 at the Federal University of Health Sciences of Porto Alegre. Along his first year of private practice he nurtured the idea of moving back to the academic field especially to learn the technique of functional magnetic resonance imaging (fMRI). Dr. Goya-Maldonado was contemplated with a DAAD scholarship to study the neural correlates of impulsivity in healthy volunteers with fMRI and achieved his doctorate in 2010 at the University of Heidelberg. Next he conducted his postdoctoral research bridging the clinical and imaging fields from 2010 to 2015 at the Max Planck Institute of Psychiatry and at the University Medical Center Göttingen (UMG), where he received grants from the UMG, BMBF and Leibniz-ScienceCampus programs. From 2016 on he leads his own research group named Systems Neuroscience and Imaging in Psychiatry (SNIP) at the UMG.

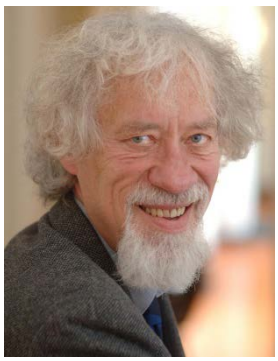
03:45 - 04:00 pm **DeepWAS: Directly integrating regulatory information into GWAS using deep learning identifies risk factors for major depressive disorder**
Fabian Theis

Fabian Theis (born 1976) studied physics and mathematics and received PhD degrees in physics and computer Science in 2002 and 2003, respectively. After working as postdoc at Regensburg, Tokyo and Tallahassee, he took up a position as Bernstein fellow at the Max-Planck Institute for Dynamics and Self-Organisation at Göttingen. He later joined the Helmholtz Zentrum Munich, first as junior group leader and since 2013 as director of the Institute of Computational Biology; since 2013 he is also full professor holding the chair 'Mathematical Modeling of Biological Systems' at the Department of Mathematics of the Technical University of Munich. His research interests include application of existing state-of-the-art machine learning algorithms and development of novel methods tailored towards solving complex biological and medical questions, in particular for modeling single cell heterogeneities, as well as multi-omics data integration in the context of systems medicine.

Wednesday, October 5, 2016 – Joint Activities - ELSA of Systems Medicine

04:30 - 05:00 pm

Medical Innovation: Handle ELSA with Care!
Wolfgang van den Daele



Wolfgang van den Daele, Dr. jur., Professor of Sociology at „Freie Universität Berlin“ until 2005 and Director of the “Division for Civil Society and Transnational Networks” at the Social Science Research Centre Berlin until 2006; member of the National Ethics Board from 2001 to 2007. Research group-fellow “ For the Constitution of Norms in Medical Ethics and Biopolitics” at Münster University.

05:00 - 05:20 pm

Acceptance of systems medicine by people at risk for mental disorders – Preliminary results of a qualitative study
Pauline Mantell

Pauline Mantell, Dipl. Ges.-Ök., studied Health Economics at the University of Cologne and the San Diego State University. Since 2013, she is research associate at the Research Unit Ethics at the University Hospital of Cologne. Her research interests include the concept and assessment of health literacy, risk prediction in the scope of mental disorders as well as palliative care in outpatient treatment. Currently, she is working on her doctoral thesis on “Health Literacy of People with Mental Health Problems”. Since 2014, she is project team member with scientific and coordinating responsibilities in the collaborative project “Systems Medicine and Health Literacy (SysKomp)”, an interdisciplinary research project of ethics, law, health system research, and psychiatry. The project is part of the thematic cluster “health literacy in complex environments” of ceres, the Cologne Center for Ethics, Rights, Economics and Social Sciences of Health.

05:20 - 05:40 pm

Translation of Systems Medicine into Clinical Routine Care – Results from an Online Survey
Martin Langanke

Dr. Martin Langanke, M.A. studied Philosophy, Theology, German Literature and Biology at Augsburg University and at the University of Erlangen-Nuremberg. In 2002 he completed his doctor thesis in the field of Philosophy of Biology. After a postdoc period and some years of professional activity in the chemical and IT industry, he works now as Senior Research Fellow at the Faculty of Theology at Greifswald University. Since 2014 he is Principal Investigator of the BMBF-funded research consortium MENON – Theoretical, normative and economical evaluation of Systems Medicine. Dr. Langanke’s areas of scientific interest are: Theoretical and normative aspects of Personalized Medicine and Systems Medicine, Animal Ethics, Moral Theory, Philosophy of Science and Medicine, Applied Research Ethics (Informed Consent, Incidental Findings, Data Protection). Dr. Langanke is member of the IF Advisory Board of the Imaging Core Center of the German National Cohort (NaCo) and Member of Advisory Board for Animal Protection Affairs of the Government of the State Mecklenburg-Western Pomerania.

Thursday, October 6, 2016 – Joint Activities - European Integration

11:00 - 11:40 am **The role of systems medicine from EC perspective**
Arnd Hoeveler

Arnd Hoeveler received his PhD from the Institute of Genetics at the University of Cologne.
In 1991 he was awarded a full Professorship in Biochemistry and Molecular Biology in France. He served several positions in France before joining the Directorate-General for Research and Innovation at the European Commission in 1996. Between 2001 and 2006 he served as Head of Unit, covering Infectious Diseases, and led several European programmes dealing with HIV/AIDS, Malaria and Tuberculosis. Since 2007 he was Head of Unit of the European Commission's Health Biotechnology programme and is now in charge of the unit 'Innovative tools, technologies and concepts in health research' dealing with Regenerative Medicine, Advanced Tools and Technologies, Systems Medicine, Predictive Toxicology, Animal Replacement Strategies and Human Biomonitoring. He is an observer on several International Advisory Boards.

11:40 - 12:10 pm **Are we seeing the beginning, or the end of Systems Medicine?**
Olaf Wolkenhauer

Olaf Wolkenhauer received his first degrees in systems and control engineering before conducting his PhD research on uncertainty modelling. He spend over ten years of his academic career in the UK, holding the first joint appointments between the biomolecular and engineering sciences at the University of Manchester. Since 2005 he holds an adjunct professorship at Case Western Reserve University, USA. In 2005, he became a fellow at the Stellenbosch Institute for Advanced Study (STIAS). Since 2003 he is professor for systems biology and bioinformatics at the University of Rostock (www.sbi.uni-rostock.de). Olaf Wolkenhauer has coordinated several national and international research consortia and is one of the initiators of the CaSyM Coordination Action for Systems Medicine. In 2015, he was elected a member of the Foundations in Medicine and Biology review panel of the German Research Foundation (DFG).

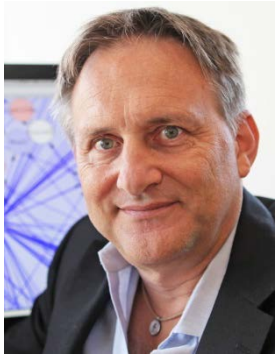
12:10 - 12:30 pm **Clinical perspective of opportunities and challenges related to multidisciplinary collaborations in systems medicine**
Mikael Benson

Mikael Benson is a professor of pediatrics and systems medicine, who directs the Centre for Personalised Medicine (CePMed) at Linköping University. The overall aim of CePMed is clinical implementation of personalised medicine based on combining big data analyses with functional and clinical studies. The focus is on T cell associated diseases, using seasonal allergic rhinitis as a primary model to develop methods to study more complex diseases. The versatility of the model has and is shown by successful applications for personalised medicine in a wide range of inflammatory diseases (Bruhn et al. Science Transl Med 2014, Gustafsson et al. Science Transl Med 2015, Nestor et al. Genome Biol 2016, Hellberg et al. Cell Reports 2016). He is an advisor to the EU directory of health for Horizon2020, the PerMed initiative and also promotes systems and personalised medicine through EASYM and CASyM.

Thursday, October 6, 2016 – Cross-topic Issues III - Therapy Response Prediction

02:00 - 02:45 pm

Keynote - Systematic elucidation and pharmacological targeting of tumor checkpoints: a new take on precision cancer medicine
Andrea Califano



Andrea Califano is the Clyde and Helen Wu Professor of Chemical Systems Biology at Columbia University Medical Center, the Founding Chair of the Department of Systems Biology, Director of the JP Sulzberger Columbia Genome Center, and Associate Director of the Herbert Irving Comprehensive Cancer Center. He is originally trained as a physicist and has applied physics-based approaches, including extensive use of information theory principles, to the reverse engineering and interrogation of gene regulatory networks to systematically and efficiently identify key tumor checkpoint modules, whose aberrant activity is necessary for tumor viability. This has resulted in several clinical trials, including a very innovative N of 1 study for precision cancer medicine. Dr. Califano has received several awards and recognitions, including the NCI Outstanding Investigator Award, fellow of the AAAS, and of the NY Academy of Medicine and Academy of Science. He is also the Co-founder of DarwinHealth Inc.

02:45 - 03:00 pm

ICT Platform for to Enable Consortium work for Systems Medicine of Heart Failure
Milena Kraus (data presented by Harry Freitas da Cruz)

Milena Kraus works as a research assistant and PhD candidate at the Hasso Plattner Institute for IT Systems Engineering (HPI) in Potsdam, Germany. In 2015, she received her diploma as an engineer of biotechnology from the Technical University of Berlin. She majored in Genetics/Biochemistry and attended several courses of the Bioinformatics Master's course of the University of Potsdam.
At the HPI, she is involved in teaching activities of bachelor's and master's curriculum, especially concerning eHealth and bioinformatics. Milena Kraus is engaged in the e:Med demonstrator project "Systems Medicine Approach for Heart Failure" (SMART) and establishes an IT platform to store, handle and analyze data acquired in the SMART observational study.
In her research she focuses mainly on the use of in-memory databases for life sciences and the analysis of heterogeneous biological data sources in the context of systems medicine.

Thursday, October 6, 2016 – Cross-topic Issues III - Therapy Response Prediction

03:00 - 03:15 pm

Bridging PET/MR Imaging and Metabolomics: Sorafenib Changes the Metabolic Profile in HCC Tumor Mouse Model
Patricia Wenk

Patricia Wenk studied Chemistry at the University of Frankfurt (2008 – 2014). During her master thesis she found her interest in methodological developments of magnetic resonance spectroscopy, specifically solid-state DNP, for biomolecular systems (presented as poster at the annual FGMR meeting 2014 (Berlin) and published, see Wenk et al, J Biomol NMR, 2015; 63(1): 97-109). Since the beginning of 2015 Patricia Wenk works on her PhD thesis at the Werner Siemens Imaging Centre, University Hospital Tuebingen. Here, her main research interest focusses on combining PET/MRI with diverse Omics techniques for oncological questions. Preclinical and clinical evaluation of tumor progression, its metabolism and treatment response in advanced liver cancer represents a central aspect. Her promising results have been presented successfully as poster or oral at the e:Med meeting 2015 (Heidelberg), DGN annual meeting 2016 (Dresden) and WMIC 2016 (New York City).

03:15 - 03:30 pm

Precision pharmacology towards the optimal treatment in lung cancer associated anemia
Agustin Rodriguez-Gonzales

My research interest was always focused on designed of new therapeutics strategies in cancer treatment. I studied Biochemistry at University of Basque Country (1992 – 1997) and obtained my PhD (1998 - 2002) in the Spanish National Research Council (IIB-CSIC). Immediately after I was employed as a Junior Scientist at the Department of R&D at Pharmamar Inc. (2003 - 2004). During 2004 I worked at the Pharmacy School of the University of Southern California (USC). The following years I was a postdoctoral researcher (2005-2007) and later on an associate researcher (2007-2008) at Jonsson Comprehensive Cancer Center (JCCC) at University of California Los Angeles (UCLA). During 2005 I was invited as scientist to the Division of Biology in the California Institute of Technology (Caltech). In 2009, I joined to DKFZ in the division “Systems Biology of Signal Transduction”, in a mixed position of postdoctoral researcher and project manager for LungSys consortium (2009-2015). Currently I am employed by German Center for Lung Research (DZL), in the multidisciplinary group of Lung Carcinoma.

Oral Presentations

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40	O - CTI I -1	Julia Fitzgerald	A knockout PINK1 model of Parkinson's disease in iPSC-derived neurons	Mito-PD
41	O - CTI I -2	Wolfgang Lieb	IBD kindred cohort: A tool for systems medicine - Kindred cohorts as a systems medicine tool for identifying causative environmental factors – Inflammatory Bowel Diseases as an example	SysINFLAME
42	O - CTI I -3	Julio Vera	A platform for the network analysis of expression data from human inflammatory macrophages in bacterial lung infections	CAPSyS
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66	O - SD II -2	Andreas J. Forstner	Identification of shared risk loci and pathways for bipolar disorder and schizophrenia	IntegraMent
68	O - SD II -3	Theo Kraus	Cell-type specific Analysis of Epigenome-Wide Methylation Differences in Schizophrenia Brains	IntegraMent
69	O - SD II -4	Roberto Goya-Maldonado	Intranasal oxytocin selectively modulates large-scale brain networks	PreNeSt
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88	O - CTI III -1	Milena Kraus / Harry Freitas da Cruz	ICT Platform for to Enable Consortium work for Systems Medicine of Heart Failure	SMART
89	O - CTI III -2	Patricia Wenk	Bridging PET/MR Imaging and Metabolomics: Sorafenib Changes the Metabolic Profile in HCC Tumor Mouse Model	Multiscale HCC
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Oral Presentations

Cross-topic Issues I - Disease Manifestation

Tuesday, October 4, 2016, 01:45 – 03:15 pm

Siri of the Cell – Intelligent agents for systems medicine constructed using systems data

Presenting Author: Trey Ideker

UC San Diego

Modern genomics is very efficient at mapping genes and gene networks, but how to transform these maps into predictive models of the cell remains unclear. Recent progress in computer science, embodied by intelligent agents such as Siri, inspires an approach for using 'omics data to seed multiscale models of the cell, which are ultimately able to predict a range of cellular phenotypes and answer biological questions.

A knockout PINK1 model of Parkinson's disease in iPSC-derived neurons

Mito-PD

Presenting Author: Julia Fitzgerald

Christine Bus (1,2,3), Benjamin Schmid (4), Susanna Hoffmann (2), Sven Geisler (2), Petra Fallier-Becker (5), Konstantina Kopoulou (6), Dilara Ozge-Halim (6), Rejko Krüger (1,2,7,8), Thomas Gasser (2,7) and Julia C. Fitzgerald (1,2,7)

1. Functional Neurogenomics Laboratory, Department of Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, Tübingen, Germany 2. The German Centre for Neurodegenerative Diseases (DZNE), Tübingen, Germany, 3. Graduate Academy of the University of Tübingen, Tübingen, Germany 4. Bioneer A/S, Hørsholm, Denmark, 5. Institute of Pathology and Neuropathology, University of Tübingen, Tübingen, Germany 6. Graduate School of Cellular and Molecular Neuroscience, University of Tübingen, Tübingen, Germany, 7. Centre for Integrative Neuroscience (CIN), University of Tübingen, Otfried-Mueller-Strasse 27, Tübingen 72076, Germany, 8. Luxembourg Centre for Systems Biomedicine, University of Luxembourg, 7 av. des Hauts Fourneaux, Esch-sur-Alzette, Luxembourg.

Parkinson's disease (PD) is a debilitating neurodegenerative disease for which there is no causative treatment. The majority of PD cases are sporadic, but rare familial forms of the disease have provided a great deal of insight into the cellular pathways underlying PD pathogenesis. One fundamental pathogenic hallmark associated with PD is mitochondrial dysfunction. The discovery of a genetic interaction between two PD genes; PINK1 and PARK2 (encoding Parkin) led to the elucidation of a highly conserved pathway that regulates mitochondrial quality control. The revolution of gene-drive systems enabled the generation of unique human neuronal models to investigate the pathological mechanism underlying PD. We have generated a PINK1 knockout in healthy human induced pluripotent stem cells (iPSCs) using TALEN-technology.and were differentiated into neurons and used to assess mitochondrial function. Ionophores induce mitochondrial removal in isogenic control cells but this effect is significantly hampered in PINK1 knockout neurons. PINK1 knockout neurons show reduced ubiquitinylation and phosphorylation of several outer mitochondrial membrane protein substrates and Parkin and exhibit severe defects in the initiation of mitophagy. As a compensatory mechanism, mitochondrial biogenesis is upregulated. As a result neurons lacking PINK1 have a significantly reduced mitochondrial membrane potential, which is less sensitive to complex I inhibitors and ionophores. Mitochondrial respiration in both PINK1 KO neurons and controls are comparable and only exhibit changes in oxygen consumption under uncoupling conditions (oxygen consumption is increased). PINK1 KO cells are more likely to utilize glycolysis and overall ATP demand is met. Apoptotic markers are dysregulated in PINK1 knockout neurons and they display increased vulnerability to the mitochondrial toxin Rotenone. PINK1 is required for Parkin-dependent mitophagy in human dopaminergic neurons, but is also important for other forms of mitochondrial quality control such as metabolism and dynamics. Using this model we are currently performing compound screening to identify pharmacological modifiers to apply novel neuroprotective strategies.

IBD kindred cohort: A tool for systems medicine - Kindred cohorts as a systems medicine tool for identifying causative environmental factors – Inflammatory Bowel Diseases as an example

SysINFLAME

Presenting Author: Wolfgang Lieb

Marie Tempel1, Gunnar Jacobs1, Femke-Anouska Heinsen2, Sandra Plachta-Danielzik1, Philip Rosenstiel2, Michael Krawczak3, Bernd Bokemeyer4, Andre Franke2, Stefan Schreiber2, Wolfgang Lieb1

1 Institute of Epidemiology/Biobank popgen, 2 Institute of Clinical Molecular Biology, 3 Institute of Medical Informatics and Statistics, all: UKSH/CAU, Kiel; 4 Gastroenterology Practice Minden; all: Germany

Background: Knowledge about the clinical and molecular predictors of inflammatory bowel disease (IBD) is limited. Family members of patients with IBD are at increased risk of developing IBD themselves. Repeated collection of health-related information, biosamples and longitudinal follow-up with respect to incident IBD in such high-risk individuals might improve the identification of molecular alterations and causative environmental factors that precede IBD.
Methods: Through local data bases with IBD patients and collaborations with patient organizations, 454 IBD patients were contacted, and invited to ask their relatives to participate in the IBD kindred cohort study. Interested unaffected and affected family members were sent questionnaires and tubes for blood and stool samples. A health-related follow-up and new collections of biosamples (blood, hair, stool) are planned every 12-18 months.
Results: Currently, 1019 individuals are participating in the cohort, 454 affected, 565 unaffected. Mean age of affected and unaffected probands are 44 ± 15.1 SD and 42 ± 19.4 SD, respectively. Currently, the cohort comprises 393 families. Family size ranges from 1 (single-proband) to 11 individuals per family. Among the affected family members, the average duration of IBD was 18 ± 12.4 SD years. From each participant, information regarding IBD-related medical history, sociodemographic characteristics, lifestyle factors, co-morbidities, therapy, dietary intake and physical activity was assessed by self-administered questionnaires at baseline. Blood and stool samples were collected according to standardized protocols. The first follow-up, including a physician questionnaire, is currently ongoing. So far, 8 new incident IBD cases have been reported within a 2- year interval. Different layers of molecular and biochemical data are being obtained, including genetic, epigenetic and microbiome data. Several molecular analyses are ongoing, comparing molecular and stool marker in affected and unaffected family members.
Conclusion: Longitudinal family studies, with repeated characterization of affected and unaffected family members over time (kindred cohorts) represent a unique tool i) to analyze familial clustering of disease pattern and ii) to identify clinical, lifestyle and molecular markers that predict the disease onset of IBD.

A platform for the network analysis of expression data from human inflammatory macrophages in bacterial lung infections

CAPSyS

Presenting Author: Julio Vera

Pia Wentker*, Martin Eberhardt*, Wilhelm Bertrams†, Kathrin Griss†‡, Florian Dreyer*, Bernd Schmeck†§, and Julio Vera*

* Laboratory of Systems Tumor Immunology, Department of Dermatology, Friedrich-Alexander University Erlangen-Nuremberg and Erlangen University Hospital Erlangen, Erlangen, Germany † Institute for Lung Research / iLung, German Centre for Lung Research, Universities of Giessen and Marburg Lung Centre, Philipps-University Marburg, Marburg, Germany ‡ Medizinische Klinik m. S. Infektiologie und Pneumologie, Charité – Universitätsmedizin Berlin, Berlin, Germany § Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Centre Giessen and Marburg, Philipps-University Marburg, Marburg, Germany

Macrophages are key players of the innate immune response against bacterial or virus infections. The mechanistic understanding of the functional modulation of macrophages by pathogens is incomplete because the fine-tuning of macrophage cellular phenotypes is governed by a tightly connected network of signaling and transcriptional pathways. The complexity of this network and the increasing amount of high throughput data sets available makes necessary the use of systems-level approaches to get comprehensive insights into macrophage regulation. We reconstructed a manually curated, validated and annotated map of signal transduction pathways involved in the activation of inflammatory macrophages. In the map, we included signalling induced by ligand-receptor interactions through interferon, MEK/ERK, IPKC/PI3K/AKT, Toll-/NOD-/RIG-like receptors, growth factors, hypoxia, chemokines, complement/integrins, interleukins, or pathogen molecules. In addition, we incorporated down-stream circuits accounting for caspase activation, transcriptional regulation, translational regulation, production of RNS/ROS/antimicrobial peptides, production of lipid mediators, and cytokines/chemokines secretion. Altogether, the reconstructed regulatory map is based upon 479 publications and comprises 842 molecule species (genes, mRNAs, miRNAs, proteins, complexes) and 814 reactions. The network is available as part of a web platform that allows the visualization, exploration, integration and mining of in vitro and in vivo HTDs. To illustrate the capabilities of the network approaches possible with our network, we selectively expanded the signaling network with database knowledge and integrated expression data from human primary cells infected with Streptococcus pneumoniae, Legionella pneumophila, or Mycobacterium tuberculosis. Through analyses of the network structure and its perturbation by pathogens, we identified a regulatory core which is regulated in all three lung infection scenarios.

Oral Presentations

Specific Diseases I - Infection & Inflammation

Tuesday, October 4, 2016, 03:45 – 03:45 pm

Intestinal Epithelial Stem Cells for the Treatment of Colitis

Presenting Author: Mamoru Watanabe

Department of Gastroenterology and Hepatology
Tokyo Medical and Dental University, Tokyo

Recent studies have expanded our knowledge of gastrointestinal stem cell biology. We have been studying colonic epithelial stem cells (Nat Med 2002, Gastroenterology 2005 & 2007). In the series of our research, we developed a novel culture method that maintains colonic stem cells in vitro. The crypt cells formed a round cystic structure consisting of epithelial monolayer of multilineage cells and could be propagated without losing their properties. Importantly, expression of Lgr5 was significantly up-regulated and then constantly maintained for a long time period. Moreover, successful, long-term engraftment was observed even with the transplantation of organoids that were derived from a single Lgr5 colon stem cell after extensive in vitro expansion in mice (Nat Med 2012). Transplanted cells readily integrated into the colonic tissues covering the area that lacked epithelium, and accelerated the recovery of recipients from acute colitis. Donor-derived cells constituted single-layered epithelium forming self-renewing donor-derived crypts that were functionally and histologically normal. We also showed that cultured cells derived from fetal gut-derived cells (Cell Stem Cell 2013) and small intestinal stem cells (Genes Dev 2014) can be transplanted in colonic tissues as stem cells. We developed our original method for human colonic epithelial cell culture from normal and colitis patients. Our data for the first time demonstrate that adult tissue stem cell therapy by in vitro expansion and transplantation of gastrointestinal stem cells could be an option for patients with severe gastrointestinal epithelial injuries such as inflammatory bowel disease in humans. New options for the treatment of ulcerative colitis by intestinal epithelial stem cells are currently under investigation by a 10-year grant from the Japan Agency for Medical Research and Development.

Quantitative modeling and simulation approaches: providing deep biological hypotheses and driving critical decisions from research through clinical trials for inflammation and immunology

Presenting Author: John M. Burke

Applied BioMath, Lincoln, MA

Systems Biology and Pharmacology (SB&P) has been used successfully in biotech and pharma. Here we show several case studies in Inflammation and Immunology, where these systems approaches enabled decisions that traditional methods could not easily address or as early or provided deep biological understanding from large data sets and complex mechanisms. SB&P models leverage known biophysical interactions and integrate data from a variety of sources (in vitro, in vivo, and clinical). SB&P models act as a central repository of data and hypotheses, allowing for predictions that cannot be fully tested prior to dosing patients.

Careful use of mathematics, modeling, analysis, simulation and visualization techniques, including dynamical systems theory and artificial intelligence approaches, and optimization, with HPC, and integration of complex biology and data to accurately model drug and disease MOA of in vitro, in vivo, and single patients and cohorts of patients to generate hypotheses for in silico pathway discovery, identify knowledge gaps, de-risk projects, and address key questions in project timelines.

We show how SB&P approaches help address critical and high value decisions or to generate testable hypotheses to better understand complex biology, allowing pharma to reduce late stage attrition rates, develop better therapeutics, faster, and for less money, that help meet unmet medical need.

Differential immune response against structural and regulatory BK virus antigens explains kinetics of BK viremia in kidney transplant patients

e:Kid

Presenting Author: Arturo Blázquez Navarro

Arturo Blázquez-Navarro 1, Dr. Thomas Schachtner 2, Dr. Ulrik Stervbo-Kristensen 1,3, Anett Sefrin 2, Prof. Dr. Timm Westhoff 3, Prof. Dr. Petra Reinke 1,2, Dr. Michal Or-Guil 4, Prof. Dr. Edda Klipp 5, Prof. Dr. Nina Babel 1,3, Prof. Dr. Avidan Uriel Neumann 1

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BK virus (BKV) associated nephropathy is a health concern affecting 1-10% of kidney transplant recipients, leading to graft failure for more than half of the cases. The only treatment comprises reducing immunosuppression to foster an anti-BKV response. We showed previously the crucial role of cellular immunity for viral clearance; however, the diverse duration of clearance in different patients is not well understood. The objective of this study is to deepen our understanding of the contribution of BKV-specific immunity to clearance by mathematical modelling. BKV-load and T-cell immunity against BKV antigens (VP1, VP2, VP3, LT and st) data from renal transplant patients upon BKV reactivation were analysed. For this, we developed an ordinary differential equation model describing the interactions between virus and immune response. The model described two modes of action: blocking virus production and killing infected cells. The result was a model showing that anti-VP response limits virus production, while anti-T induces accelerated death of infected cells. The model offered evidence for low viral cytopathicity, contrary to existing consensus, suggesting that BKV might be lysogenic under certain circumstances This is the first model for BKV which incorporates simultaneously the influence of the immune system with the viral dynamics; as well as the first that models an immune response against a virus through two different action modes mediated by different antigens. Our model can also be applied to study the correlation between immune dynamics and different therapies, improving BKV infection management and reducing kidney transplant rejections.

Uncoupling of Mucosal Gene Regulation, Splicing and Microbiota Signatures in Inflammatory Bowel Disease

SysINFLAME

Presenting Author: Raheleh Sheibani

Robert Häsler (1), Raheleh Sheibani-Tezerji (1), Anupam Sinha (1), Matthias Barann (1), Ateequr Rehman (1), Daniela Esser (2), Konrad Aden (1), Carolin Knecht (3), Berenice Brandt (4), Susanna Nikolaus (4), Sascha Schäuble (5), Christoph Kaleta (2), Andre Franke (1), Christoph Fretter (6), Werner Müller (7), Marc-Thorsten Hütt (6), Michael Krawczak (3), Stefan Schreiber (1, 4), Philip Rosenstiel (1)

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Objective: An inadequate host response to the intestinal microbiota likely contributes to the manifestation and progression of human inflammatory bowel disease (IBD). However, molecular approaches to unravelling the nature of the defective crosstalk and its consequences for intestinal metabolic and immunological networks are lacking. We assessed the mucosal transcript levels, splicing architecture and mucosa-attached microbial communities of IBD patients to obtain a comprehensive view of the underlying, hitherto poorly characterized interactions, and how these are altered in IBD. Design: Mucosal biopsies from Crohn's disease and ulcerative colitis patients, disease controls and healthy individuals (n=63) were subjected to microbiome, transcriptome and splicing analysis, employing next generation sequencing. The three data levels were integrated by different bioinformatic approaches, including systems biology-inspired network and pathway analysis. Results: Microbiota, host transcript levels and host splicing patterns were influenced most strongly by tissue differences, followed by the effect of inflammation. Both factors point towards a substantial disease-related alteration of metabolic processes. We also observed a strong enrichment of splicing events in inflamed tissues, accompanied by an alteration of the mucosa-attached bacterial taxa. Finally, we noted a striking uncoupling of the three molecular entities when moving from healthy individuals via disease controls to inflammatory bowel disease patients. Conclusion: Our results provide strong evidence that the interplay between microbiome and host transcriptome, which normally characterizes a state of intestinal homeostasis, is drastically perturbed in Crohn's disease and ulcerative colitis. Consequently, integrating multiple OMICs levels appears to be a promising approach to further disentangle the complexity of IBD.

Oral Presentations

Cross-topic Issues II - Heterogeneity of Disease

Wednesday, October 5, 2016, 09:00 – 10:30 am

Presenting Author: Elaine Holmes

Imperial College London

Classification of pediatric glioblastoma according to their telomere maintenance features

CancerTelSys

Presenting Author: Inn Chung

Inn Chung(1), Katharina I. Deeg(1), Delia Braun(1), Alexandra M. Poos(2), Andrey Korshunov(3,4), Jacques Grill(5), Rainer König(2), Stefan M. Pfister(6,7), David T.W. Jones(6), and Karsten Rippe(1,*)

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Pediatric glioblastoma (pGBM) are highly aggressive brain tumors (WHO grade IV) with poor prognosis. Recent studies on pGBM have revealed recurrent mutations in the genes encoding the chromatin remodeler ATRX and the histone variant H3.3. Mutations in ATRX strongly correlate with activation of the alternative lengthening of telomeres (ALT) pathway, a telomere maintenance mechanism (TMM) that is prevalent in pGBMs, and ATRX has been shown to suppress ALT. To date, however, telomere features of pGBMs have not been studied in detail and model cell lines that represent different active TMMs in pGBMs are lacking. Here we systematically characterized seven pGBM cell lines that carry a representative set of recurrent genomic mutations as well as 57 primary tumor samples with respect to features relevant for the TMM. We evaluated the telomere length distribution, telomere repeat content, phosphorylation of histone H3.3 at serine 31 (H3.3S31p), the presence of ALT-associated promyelocytic leukemia (PML) nuclear bodies (APBs) and C-circles, which are a specific type of extrachromosomal telomeric repeats, as well as genome sequences and RNA expression profiles. Based on these features we developed a classification scheme that predicts the probability of ALT from combinations of the cytogenetic and/or genomic data available. Together, our findings elucidate the ALT pathway in pGBMs and provide valuable cell line models for evaluating ALT targeted therapies in a preclinical setting.

Genome-wide host-microbiota association analysis of 1,812 individuals identifies vitamin D receptor genetic variation and other host factors shaping the gut microbiota

SysINFLAME

Presenting Author: Andre Franke

Jun Wang1,2,#, Louise B. Thingholm3,#, Jurgita Skiecevičienė3,#, Philipp Rausch1,2, Martin Kummen4,5,6, Johannes R. Hov4,5,6,7, Frauke Degenhardt3, Femke-Anouska Heinsen3, Malte C. Rühlemann3, Silke Szymczak3,†, Kristian Holm4,5,6, Tönu Esko8, Jun Sun9, Mihaela Pricop-Jeckstadt10, Samer Al-Dury11, Pavol Bohov12, Jörn Bethune3, Felix Sommer3, David Ellinghaus3, Rolf K. Berge12,13, Matthias Hübenthal3, Manja Koch14, Karin Schwarz15, Gerald Rimbach15, Patricia Hübbe15, Wei-Hung Pan3, Raheleh Sheibani3, Robert Häsler3, Philipp Rosenstiel3, Mauro D'Amato16,17, Katja Cloppenborg-Schmidt2, Sven Künzel1, Matthias Laudes18, Hanns-Ulrich Marschall11, Wolfgang Lieb14, Ute Nöthlings10, Tom H. Karlsen4,5,6,7,19, ‡, John F. Baines1,2, ‡, Andre Franke3, ‡*

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# These authors contributed equally to this work.

‡ These authors jointly supervised this work.

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The human gut microbiota is an important determinant for health and disease, and recent studies emphasize the numerous forces shaping its diversity. Here, we performed a genome-wide association study (GWAS) of the gut microbiota using two northern-German cohorts

totaling 1,812 individuals. Comprehensively controlling for diet and non-genetic parameters, we identify genome-wide significant associations for overall microbial variation and individual taxa at multiple genetic loci, including the Vitamin D Receptor (VDR). We observe significant shifts in the microbiota of Vdr-/- mice and correlations between the microbiota and serum measurements of selected human bile- and fatty acids, including known ligands and downstream metabolites of VDR. Genome-wide significant associations at multiple additional loci reveal other important points of host-microbial intersection, notably several disease susceptibility genes and sterol metabolism pathway components. Non-genetic and genetic forces each account for approximately 10% of the variation in the gut microbiota, whereby individual effects are relatively small.

Abundance vector shifts under Boolean operations reveal systematic interactions of low-abundance species in the human gut microbiome

SysINFLAME

Presenting Author: Jens Christian Claussen

Jens Christian Claussen, Jurgita Skieceviciene, Jun Wang, Philipp Rausch, Tom H. Karlsen, Wolfgang Lieb, John Baines, Andre Franke and Marc-Thorsten Hütt

Computational Systems Biology Lab, Jacobs University Bremen, Germany; Institute for Clinical Molecular Biology, Christian-Albrecht University Kiel, Germany; Lithuanian University of Health Sciences, Kaunas, Lithuania; Laboratory of Molecular Bacteriology, University of Leuven; Max-Planck-Institute for Evolutionary Biology, Plön, Germany: Institutt for indreminisinisk forskning, Oslo, Norway: Institute of Epidemiology, Christian-Albrechts-University Kiel, Germany

The analysis of microbiome compositions in the human gut has gained increasing interest due to the broader availability of data and functional databases and substantial progress in data analysis methods, but also due to the high relevance of the microbiome in human health and disease. While most analyses infer interactions among highly abundant species, the large number of low-abundance species has received less attention. Here we present a novel analysis method based on Boolean operations applied to microbial co-occurrence patterns. We validate our approach with simulated data based on a dynamical Boolean network model from which we interpret the statistics of attractor states as a theoretical proxy for microbiome composition. We show that for given fractions of synergistic and competitive interactions in the model our Boolean abundance analysis can reliably detect these interactions. Analyzing a novel data set of 822 microbiome compositions of the human gut, we find a large number of highly significant synergistic interactions among these low-abundance species, forming a connected network, and a few isolated competitive interactions.

Oral Presentations

Specific Diseases II - Neuropsychiatric Disorders

Wednesday, October 5, 2016, 02:00 – 04:00 pm

A systems medicine approach for better understanding of alcohol addiction

Presenting Author: Wolfgang H. Sommer

ZI Mannheim

Alcohol addiction is a major public health challenge in need of new treatments. The disorder is characterized by periods of excessive drinking, interspersed with variable intervals of abstinence, and frequent relapses, the latter being the key focus of therapeutic efforts. As alcoholism evolves, the function of distinct brain system is altered, but the neurobiological mechanisms underlying these changes and their potential for recovery are poorly understood.
Here I present two initiatives, SysMedAlc (e:Med, http://www.sysmedalc.eu) and SyBil-AA (Horizon2020, http://sybil-aa.eu), both using discovery strategies based on the principles of systems medicine by using mathematical and network models to identify mechanisms that can be targeted specifically by therapeutic interventions. SysMedAlc exploits various –omics datasets to identify individual neurobehavioral risk profiles in adolescents, that are predictive of alcohol use disorders later in life, as well as in alcoholic patients, and that may identify targetable pathways. SyBil-AA focusses on functional magnetic resonance imaging (fMRI) data from patients and alcohol dependent animals as a basis for building predictive models of the 'relapse-prone' state of brain networks. The information on molecular pathways and brain network components that promote 'relapse-proneness' will be used to design optimized pharmacotherapies. Both projects rely on rigorous testing by experimental model validation in animals and humans. The challenge ahead is to combine these multi-level investigations into a common framework for rational development of novel therapies.

Exome sequencing of European families densely affected with bipolar disorder reveals rare variants in neuronal genes contributing to disease etiology

IntegraMent

Presenting Author: Anna Maaser

Anna Maaser1,2, Jana Strohmaier3 , Kerstin U. Ludwig1,2, Franziska Degenhardt1,2, Fabian Streit3, Lorena M. Schenk1,2, Anna C. Koller1,2, Sascha B. Fischer4, Holger Thiele5, Peter Nürnberg5, Jose Guzman Parra6, Guillermo Orozco Diaz7, Georg Auburger8, Margot Albus9, Margitta Borrmann-Hassenbach9, Maria José González10, Susana Gil Flores11, Francisco J. Cabaleiro Fabeiro12, Francisco del Río Noriega13, Fermin Perez Perez14, Jesus Haro González15, Fabio Rivas41, Fermin Mayoral16, Stefan Herms1,2,4, Per Hoffmann1,2,4,17, Sven Cichon1,2,4,17, Marcella Rietschel3, Markus M. Nöthen1,2, Andreas J. Forstner1,2

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Bipolar disorder (BD) is a major psychiatric disorder affecting more than 1% of the world's population. The highly heritable disease is characterized by recurrent episodes of manic and depressive symptoms.
As the cumulative impact of common alleles with small effect may only explain around 38% of the phenotypic variance for BD, rare variants of high penetrance have been suggested to contribute to BD susceptibility.
In the present study we investigated 210 individuals of 68 large multiply affected families of German and Spanish origin using whole exome sequencing (Illumina HiSeq2500 platform). For data analysis the Varbank pipeline of the Cologne Center for Genomics was used. We filtered for rare (minor allele frequency <0.1%) and non-synonymous variants that are shared within each family and are predicted to be damaging by at least four of five different bioinformatics tools.

We identified a total of 1214 rare, segregating and potentially damaging variants implicating 1122 different genes. Pathway analysis of 342 genes with a Residual Variation Intolerance Score <25% showed a significant enrichment ($p<0.001$) for 18 pathways including neuron development and post synaptic density. Furthermore, 75 genes were implicated by rare variants in at least two unrelated families. These comprise NRXN2 which encodes a synaptic cell-adhesion molecule connecting pre- and postsynaptic neurons and mediating synaptic signaling as well as CDH22 and CDH7 that encode calcium-dependent cell-adhesion proteins. The former may play an important role in neural morphogenesis in the developing brain and variants in CDH7 may be associated with multiple psychiatric disorders.
Our preliminary results suggest that rare and highly-penetrant variants in genes involved in synaptic signaling and cell-adhesion contribute to BD development. Follow up analyses of the implicated genes in independent case/control samples are currently underway and will be presented at the upcoming meeting.

Identification of shared risk loci and pathways for bipolar disorder and schizophrenia

IntegraMent

Presenting Author: Andreas J. Forstner

Andreas J. Forstner1,2,3,4, Julian Hecker5, Andrea Hofmann1,2,6, Anna Maaser1,2, Céline S. Reinbold4, Thomas W. Mühleisen1,2,4,7, Markus Leber8, Jana Strohmaier9, Franziska Degenhardt1,2, Jens Treutlein9, Manuel Mattheisen1,10,11, Fabian Streit9, Stefan Herms1,2,4, Per Hoffmann1,2,4, Stephanie H. Witt9, Bertram Müller-Myhsok12,13,14, Thomas G. Schulze15, Marcella Rietschel9, Sven Cichon1,2,4,7, Heide Fier5, Markus M. Nöthen1,2

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Bipolar disorder (BD) is a highly heritable disorder of mood with a lifetime prevalence of about 1%. BD shows substantial clinical and genetic overlap with other psychiatric disorders, particularly with schizophrenia (SCZ). However, research has not yet clarified what particular genes form the basis of this etiological overlap. For both disorders several susceptibility genes have been identified. In the case of SCZ, a meta-analysis (36000 patients, 113000 controls) of the Psychiatric Genomics Consortium (PGC) identified 128 independent genome-wide significant SNPs. The aim of the present study was to investigate whether these 128 SCZ-associated SNPs also contribute to BD development. For this purpose, we conducted association testing in our large GWAS dataset of BD (9747 patients, 14278 controls, Mühleisen et al., 2014). In this dataset we combined our data with the BD GWAS results of the PGC (Sklar et al., 2011). As different reference panels were used for the imputation of the genotype data in both studies, we reimputed the summary statistics of the PGC BD GWAS using ImpG-Summary (Pasaniuc et al., 2014). Overall, 107 SCZ-associated SNPs could be mapped to our reimputed data. A meta-analysis for these 107 SNPs was then performed using METAL. To correct for an overlap of around 500 patients and 9200 controls between our BD GWAS and the PGC SCZ GWAS, the correlation of z-scores between both studies was calculated using the LD Score regression method (Bulik-Sullivan et al., 2015). After re-imputation and correction for sample overlap, 22 of 107 investigated SCZ-SNPs showed

nominal association with BD (p=1.46x10-8). Two SNPs (rs75968099, rs2535627) remained significant after Bonferroni correction. Pathway analyses for all shared SCZ-BD SNPs revealed 25 nominally significant pathways, including synaptic long term potentiation, calcium- and glutamate signaling. Our findings suggest new research directions for the treatment and prevention of BD and SCZ.

Cell-type specific Analysis of Epigenome-Wide Methylation Differences in Schizophrenia Brains

IntegraMent

Presenting Author: Theo Kraus

Theo Kraus [1], Andrea Schmitt [2], Judith Spanner [1], Anne Hartebrodt [1], Peter Falkai [2], Armin Giese [1]

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The epigenome exerts essential influence on the regulation of cellular processes. One of the most important epigenomic mechanisms is the methylation of cytosine in the DNA sequence leading to an inactivation of transcription. Aberrant promoter methylation has been identified as cause for numerous diseases. Recent research emphasises that alterations of the epigenome lead to the development of numerous psychiatric diseases such as schizophrenia. As the epigenome is cell type specific, epigenomic studies require the analysis of the target tissue. Analysing human post-mortem brain samples we were confronted with the fact that the brain consists of a mixture of numerous different cell types. Facing this challenge, we developed an advanced cell separation technique that we called FIONA (Fluorescence-assisted Isolation Of Nuclear Assemblies). FIONA enables us to separate distinct cell populations for human post-mortem brain tissue with purities of at least 95%. To analyze the cell type specific epigenomes of neuronal and non-neuronal cells in the prefrontal (BA 10) and occipital (BA 17/18) cortex of human control and schizophrenia brains we combined FIONA with epigenome wide methylation profiling using next generation sequencing (NGS). We found that neurons and non-neuronal cells possess distinct epigenome-wide methylation signatures. Performing computational analysis, we identified cell type specific differentially methylated CpGs (DMCG) being associated with genes across all autosomal chromosomes. Analysis of methylation differences in cell populations of schizophrenia patients showed that there are distinct methylation differences in neurons of schizophrenia brains. In summary, our integrated analysis demonstrated cell type specific methylation profiles and highlighted distinct methylation differences in schizophrenia brains revealing new potential pathways contributing to the development of schizophrenia.

Intranasal oxytocin selectively modulates large-scale brain networks

PreNeSt

Presenting Author: Dr. Roberto Goya-Maldonado

Katja Brodmann, Oliver Gruber, Roberto Goya-Maldonado

Systems Neuroscience and Imaging in Psychiatry, Department of Psychiatry and Psychotherapy, University Medical Center Göttingen

A growing body of evidence indicates that the neuropeptide oxytocin (OT) alters the neural correlates of socio-emotional and salience processing. Yet the effects of OT over the large-scale networks involved in socio-emotional and salience processing, namely the default mode (DM), ventral attention (VA) and cingulo-opercular (CO) networks, remain unknown. Therefore, we conducted a placebo-controlled crossover study with intranasal 24IU OT in 38 healthy male subjects using a resting-state fMRI (rs-fMRI) paradigm to investigate the three network candidates. To fundamentally understand the underlying mechanisms of the neuropeptide, we compared the intra-network connectivity for each network candidate and also the inter-network connectivity across all networks between both treatment groups. Based on the relevance of inter-individual factors for OT effects, we additionally correlated individual network changes with impulsivity scores. Our results show that OT mainly alters the connectivity in the VA network, from one side reducing the coupling to regions that typically form the DM nodes, an introspective and self-referential network, and from the other side increasing the coupling to the edges of the CO network, which is involved in salience processing. The results of the inter-network analyses confirmed the specificity of the OT effects. Additionally, connectivity changes in key-regions of the reward system for each subject significantly correlated with their impulsivity scores. Overall, our data supports that the modulation of functional connectivity within the VA network is a basic mechanism by which OT directs attentional resources from internal to external cues, preparing the brain for contextual-dependent salience processing. Understanding the network modulation driven by OT is imperative for development of more promising interventions to clinical conditions in which impaired social salience processing occur.

DeepWAS: Directly integrating regulatory information into GWAS using deep learning identifies risk factors for major depressive disorder

e:AtheroSysmed, IntegraMent, SYS-Stomach

Presenting Author: Fabian Theis

Gökcen Eraslan*,1, Janine Arloth*,1,2, Jade Martins2, Stella Iurato2, Darina Czamara2, Elisabeth B. Binder2,4, Fabian J. Theis1,3, Nikola S. Mueller1

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Genome-wide association studies (GWAS) identify genetic variants predictive of common diseases but this does not directly inform on molecular mechanisms. The recently developed deep learning-based method DeepSEA uses DNA sequences to predict regulatory effects for up to 1000 functional units, namely regulatory elements and chromatin features in specific cell-types from the ENCODE project. We here describe “DeepWAS”, a new GWAS approach that integrates these predictions to identify SNP sets per functional units prior to association analysis based on multiple regression. To test the power of this approach, we use genotype data from a major depressive disorder (MDD) case/control sample. DeepWAS identified 177 regulatory SNPs moderating 122 functional units. Joint integrative analysis of regulatory SNPs and the independently identified annotations were connected through transcription factors MEF2C and others, regulating a network of transcripts previously linked to other psychiatric disorders. This finding, complementary to recent depression GWAS data, underlines the power of DeepWAS.

Oral Presentations

ELSA of Systems Medicine

Wednesday, October 5, 2016, 04:30 – 05:40 pm

Medical Innovation: Handle ELSA with Care!

Presenting Author: Wolfgang van den Daele

Wissenschaftszentrum für Sozialforschung, Berlin

The ELSA program is part of the reflexive turn which innovation policies have taken in recent decades in order to enhance early public awareness of and regulatory responses to the prospects and challenges of new technologies. The underlying premise is that ELSA – and other programs such as „Responsible Innovation“ and technology assessment in general - will contribute to the social integration and acceptance of innovation. Their actual effects are, however, ambivalent. They may also lead to undue hurdles: by excessive demands for precautionary risk control, by escalating public mistrust in established regulatory institutions, by devaluating expert knowledge and professional competence.

ELSA for biomedicine may be less susceptible to such aberrations. Fundamental criticism and rejection are unlikely to emerge because science and technology for medical purposes is generally accepted as desirable and legitimate. Especially with regard to the translation of systems medicine into clinical practice the questions and problems raised within the ELSA perspective are, on the contrary, largely quite conventional and dealt with through existing professional routines: defining criteria for predictive testing, finding thresholds for preventive intervention when risk factor indicate the probability of disease in the future, securing the informed consent and non-directive counseling of patients who belong to the ‚healthy ill'.

Conventional problems remain real problems; and they deserve further reflection and analysis. But ELSA projects try to go beyond the conventional to demonstrate their specificity and relevance. For instance, they investigate on the micro-level the psychodynamics of communication and information-processing in the patient-physician-relationship; and they extend on the macro-level the analysis to issues such as the cultural meaning of health, the power dimensions implied in professional roles, or the economics and social justice in the system of health care. While such inquiries may yield valuable insight into the complexity of medical communication and into the social and political embeddedness of medicine, their impact on the clinical application of systems medicine will be (and should be) quite limited. The professional routines applied so far can deal with the upcoming problems, and they are likely to take the lead. And patient autonomy will continue to be the crucial focus of regulatory intervention.

Acceptance of systems medicine by people at risk for mental disorders – Preliminary results of a qualitative study

SysKomp

Presenting Author: Pauline Mantell

Universität zu Köln

Systems medicine arouses hope to bring forward the long desired paradigm shift towards prevention in the health care system. This will become particularly important for people with mental distress since the research and development of medical risk profiles and early detection measures of mental disorders progress rapidly. However, people at risk need to know how to make use of these possibilities in order to receive individual benefits. Individual acceptance and motives of potential use and rejection of systems medicine are essential for achieving reasonable establishment.

In this cross-sectional analysis, we estimate the acceptance of systems medicine by people at risk for mental disorders. Items consist of two open questions regarding systems medicine approaches in prediction and prognosis. We controlled for general health literacy, socio-demographic and psychopathological characteristics of the sample. Preliminary results include answers from 131 individuals with mental distress seeking help at an early detection center for mental disorders in Cologne, Munich and Dresden.

Participants tend to have very clear positions whether to use or reject systems medicine, overall accepting prognosis approaches more than predictive ones. Risk perception as a potential psychological burden is one of the major reasons for a decline of acceptance. The desire for self-determination and self-responsibility is a major reason for refusal as well as for approval. A striking difference is revealed in motives concerning a desire of control versus the fear of loss of control.

In terms of a future-oriented implementation of systems medicine, acceptance and motives of individuals must be taken into account and competencies increased where necessary. Health literacy is considered a key concept to positively address challenges of navigating the health care system and making autonomous decisions concerning health.

Translation of Systems Medicine into Clinical Routine Care – Results from an Online Survey

MENON

Presenting Author: Martin Langanke

Pia Erdmann1, Tobias Fischer2, Martin Langanke1,2

1 Faculty of Theology, Systematic Theology, University of Greifswald, Greifswald, Germany

2 Institute for Ethics and History of Medicine, University Medicine Greifswald, Greifswald, Germany

Systems medicine is the name for an assemblage of scientific strategies and practices that include
bioinformatics approaches to human biology (especially systems biology); “big data” statistical analysis; and medical informatics tools. Whereas personalized and precision medicine involve similar analytical methods applied to genomic and medical record data, systems medicine draws on these as well as other sources of data. Given this distinction, the clinical translation of systems medicine poses a number of important ethical and epistemological challenges for researchers working to generate systems medicine knowledge and clinicians working to apply it.
Against this background the BMBF-funded ELSI consortium “MENON – Theoretical, normative and economic implications of systems medicine” is investigating three key challenges: First, MENON is examining the conflicts in decision-making that can arise when healthcare providers committed to principles of experimental medicine or evidence-based medicine encounter individualized recommendations derived from computer algorithms. We are exploring in particular whether controlled experiments, such as comparative effectiveness trials, should mediate the translation of systems medicine, or if instead individualized findings generated through “big data” approaches can be applied directly in clinical decision-making. Second, MENON is investigating the ethical challenges that can arise when big-data-driven scoring systems are applied in clinical contexts. Third, we build on the recent discourse on secondary findings in genomics and imaging to draw attention to the important implications of secondary findings derived from the joint analysis of data from diverse sources, including data recorded by patients in an attempt to realize their “quantified self.”
To bridge the gap between the sphere of theoretical and ethical analyses and the “real world” of current research in systems medicine, the MENON consortium launched an online survey to ask experts from “e:Med – Systems Medicine” about their perspectives, assumptions and estimations regarding these three topics of interest. Quantitative and qualitative data from this survey, which was performed between March and May 2016, will be presented in our talk and preliminary conclusions will be discussed with the audience.

Oral Presentations

European Integration

Thursday, October 6, 2016, 11:00 – 12:30 pm

Are we seeing the beginning, or the end of Systems Medicine?

Presenting Author: Olaf Wolkenhauer

University Roststock

Depending on the country you live in and depending on the scientific community you belong to, "precision medicine", "personalized medicine", "big data for health", and "systems medicine" are a selection of terms used to describe changes in medical research. Various initiatives are preparing 'position statements', 'road maps', 'action plans', guiding funding bodies on how to support research and development for better diagnosis, prognosis, therapy and prevention of diseases. While I share the excitement for the science that is behind these different terms, I am very worried that these different groups develop a competition that could threaten our common goals.

The communities of epidemiology, medical informatics, bioinformatics and systems biology should not be in competition for how to advance medical research. Of course, it does make sense to make distinctions, say between bioinformatics and medical informatics and we will or should continue to visit different conferences and publish in different journals, and yet, working towards a better diagnosis, prognosis and therapy, their approaches must come together! The competition should therefore not be about alternative approaches but about how we best integrate them. My personal hope has been that Systems Medicine would be the umbrella under which we come together but recent developments show that this is rather difficult.

Funding programmes can continue to target different communities but there must also be an effort to create a better awareness of what is going on in these different fields. We need to create opportunities for the researchers from these communities to come to together in multi and interdisciplinary consortia. I hope it is not too late to realise the need for a joint effort, whatever term we use to describe this integration.

Clinical perspective of opportunities and challenges related to multidisciplinary collaborations in systems medicine

Presenting Author: Mikael Benson

Linköping University

Some of the most important challenges in today's health care are not likely to be solved by focusing on individual diseases and genes. One key challenge is that a large number of patients do not respond to treatment. This causes great suffering and enormous costs. Reasons include the involvement of thousands of genes in combinations that vary between patients that do or do not respond to a given treatment. Those variations are in turn associated with different comorbidities, gender and environmental factors. Ideally, physicians should understand and be able to determine such variations for personalised medicine (PM). It is likely that this will lead to diagnostic re-classification. Because of the importance of comorbidities it would ideally be necessary to start on a population-wide scale to identify different disease combinations and their associated molecular and environmental mechanisms. This can be done based on combined mining "big" data like population-wide electronic medical records and omics data in the public omics data. The next step would be to zoom in on functional and clinical studies of selected disease combinations in order to find markers of variations, which are suitable for PM. This requires multi-disciplinary collaborations between experts in epidemiology, omics, bioinformatics and domain-specific functional and clinical researchers. We have recently published strategies for such studies aiming at PM (Bruhn et al. Science Transl Med 2014, Gustafsson et al. Science Transl Med 2015).
Based on those experiences it is optimal to have a clinician-led core multi-disciplinary group working in the same location, which is closely linked to the clinic, and also to leading international experts.

Oral Presentations

Cross-topic Issues III –
Therapy Response Prediction

Thursday, October 6, 2016, 02:00 – 03:30 pm

Systematic elucidation and pharmacological targeting of tumor checkpoints: a new take on precision cancer medicine

Presenting Author: Andrea Califano

Columbia University, New York

Use of targeted inhibitors in precision cancer medicine is largely predicated on the identification of actionable oncogene mutations. Yet, only ~25% of human malignancies present with actionable alterations, and only a small fraction of these present with long term clinical benefit. Indeed, most of the patients who initially respond eventually relapse with drug-resistant disease. Thus, there is urgent need for complementary precision cancer medicine approaches that focus on protein targets representing individual and synergistic tumor vulnerabilities, independent of their mutational status.

To address this challenge, we have developed network-based methods for the systematic identification and validation of tumor checkpoint modules, comprising Master Regulator proteins, whose concerted aberrant activity is both necessary and sufficient to implement and maintain tumor cell state. We have identified and validated tumor checkpoints for multiple tumor types, from glioblastoma and lymphoma to breast and prostate adenocarcinoma and shown that they implement complex regulatory bottlenecks, whose genetic or pharmacologic inhibition abrogates tumor viability in vitro and in vivo. Finally, we have developed methodologies that leverage large-scale drug-perturbation assays to systematically elucidate drugs and drug combinations that abrogate tumor checkpoint activity, on an individual patient basis. To systematically evaluate this approach, we have opened a novel N-of-1 study, which is currently enrolling 260 patients across 14 rare or incurable tumor subtypes. Patients are studied on an individual basis to identify their critical tumor checkpoint dependencies, as well as the drugs and drug-combinations that are optimally suited to abrogate their activity in vivo. Therapeutic value is then evaluated in patient-derived xenografts (PDX) and/or organotypic cultures and ultimately used to guide patient therapy.

ICT Platform for to Enable Consortium work for Systems Medicine of Heart Failure

SMART

Presenting Author: Harry Freitas da Cruz

Milena Kraus, Matthieu-P. Schapranow

Hasso-Plattner-Institute Potsdam

Applying systems medicine requires established processes, e.g. to exchange data, to understand and reproduce results based on these data, and trigger process steps based on events. We share details of our software system architecture for system medicine designed in our “Systems Medicine of Heart Failure” (SMART) consortium. We modeled selected software components using the Fundamental Modeling Concepts. The core of our SMART software platform is the In-Memory Database (IMDB), which has proven to be able to analyze big medical data in real time and integrate heterogeneous data sources. All SMART partners located at individual research institutes create specific data artifacts about heart failure patients enrolled in SMART study. The sync agent ensures immediate integration of newly created or updated data from partner locations into the central IMDB instance. As a result, our SMART platform automatically notifies relevant user groups about available data in our SMART platform and triggers next process steps. Thus, researchers and clinicians can logon to our SMART platform via secured web applications to access the data, analyze them, and take corresponding actions. Specific applications address, amongst others,the processing and real-time analysis of raw RNA data, proteome data, and interactive multi-scale modeling. These features are based on work of the SMART consortium members and are integrated in close collaboration. We shared details about SMART ICT platform, specific design decisions, and introduced selected features supporting system medicine in a clinical context. Thus, it streamlines the clinical systems medicine process by integrating distributed data artifacts into a central database instance, triggering process events, and real-time data analysis functions.

Bridging PET/MR Imaging and Metabolomics: Sorafenib Changes the Metabolic Profile in HCC Tumor Mouse Model

Multiscale HCC

Presenting Author: Patricia Wenk

P. Wenk1, F. Heinzmann2, S.M.M. Ud-Dean1, T-W. Kang2, J.Cotton1, G. Bowden1, G.Reischl1, L. Zender2, A. M. Schmid1, B. J. Pichler1

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

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer related death, mainly due to lack of treatment options, adapted resistance and tumor heterogeneity. Thus, evaluation of tumors' molecular profiles during progression and treatment in a mouse model similar to human HCCs is required for clinical translation. C-myc + N-RasG12V or Akt-1 driven HCCs in Sorafenib or vehicle-treated, female wt mice (n=~4 /group), were analyzed longitudinally by weekly combined PET/MRI. Dynamic PET with [18F]FDG or [18F]FMISO (80 or 180 min) were performed addressing glucose consumption and hypoxia, T2-weighted MRI served as anatomical reference. Multiple regions of interest (ROIs) were drawn via hot-spot analysis and tracking later tumor progression by their molecular behavior. Finally, tissue samples were prepared for NMR metabolomics, autoradiography and histology. Control and treated mice showed high glucose consumption in tumorous liver tissue, while hypoxic lesions mainly occurred in treated mice. Hot-spot-analysis indicated striking differences in time-activity-curves (TACs). While for control mice all ROIs varied strongly in shape and amplitude e.g. for tumors yielding low and high uptake regions (4.0 to 9.9 %ID/mL), in treated lesions this diversity is heavily reduced. Autoradiography and histology confirmed compelling differences in tumor progression and tracer uptake. Interestingly, metabolomics showed a significant increase of fatty acids for treated mice depending on the genetic origin, which pinpoints a stimulated lipid metabolism as potential resistance mechanism. We could visualize the remarkable impact of Sorafenib treatment towards a more uniform HCC progression and metabolic profile, depending on the genetic origin. This is a major step in understanding the genetic and metabolic connection of tumor development and therapy resistance and bridge imaging and metabolomics to deliver relevant information to optimize tumor therapy.

Precision pharmacology towards the optimal treatment in lung cancer associated anemia

Presenting Author: Agustin Rodriguez-Gonzalez

Agustin Rodriguez-Gonzalez(1,2,3), Max Schelker(4,5), Andreas Raue(4,9), Bernhard Steiert(4), Florian Salopiata(1,3), Lorenz Adlung(1), Martin E. Böhm(1), Markus Stepath(1), Sofia Depner(1,2,3), Marie-Christine Wagner(1), Ruth Merkle(1,3), Bernhard A. Kramer(1), Susen Lattermann(1), Marvin Wäsch(1,3), Andreas Franke(6), Edda Klipp(5), Patrick Wuchter(7), Anthony D. Ho(7), Wolf D. Lehmann(1), Michael Jarsch(6), Marcel Schilling(1), Jens Timmer(4,8) and Ursula Klingmüller(1,2,3)

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Background: With 1.8 million of new cases per year, Lung Carcinoma (LC) is globally the cancer with the highest incidence. The prevalence of anemia in LC ranges from 50% to up to 90% in the most advanced stages. Cancer associated anemia reduces the response to chemotherapy and the quality of life. Erythropoiesis Stimulating Agents (ESAs) have been widely used to correct anemia in cancer, however 30-50% of the patients do not respond to ESA treatment, and mortality risk is increased. The low efficiency of ESAs treatment together with the safety concerns constitutes a complex question that requires a systems biology approach to treat anemia in cancer. Method: We combined a dynamic pathway model on the interaction of ESAs with the erythropoietin receptor (EpoR) with quantitative data from pharmacokinetic and pharmacodynamic experiments of ESAs in human subjects. We utilized coupled ordinary differential equations (ODE) that link the cellular scale with the body scale and calibrated the model parameters based on quantitative experimental determinations determined at multiple experimental scales. Results: The ODE model was able to describe the dynamic interaction of ESAs at molecular, cellular and systemic level in the human body. Further, the ODE model enabled to predict optimal dosing for ESAs to preferentially activate the EpoR in the hematopoietic context but not in the tumor context. Conclusion: This model can describe the binding properties, dynamic interaction and the pharmacokinetic-pharmacodynamics of any EpoR ligand, and predict efficient and safer ESA concentrations optimized for the individual lung cancer patient.

Company lunch talks
Abstracts

RNA-Seq and DNA-Seq from Picogram Inputs

Presenting Author: Dr. Martin Heine, Technical Support Scientist

NuGEN

RNA-Seq and DNA-Seq applications are expanding to a wide array of different sample types, requiring the need for greater system sensitivity. For example, RNA-Seq analyses of transcripts from large numbers of cells often mask biologically relevant differences that occur in individual cells. Understanding RNA expression in a single cell has great potential for biomarker development, monitoring of disease progression, and response to therapies. A novel approach has been developed for generating stranded total RNA-Seq libraries from single human cells or from input amounts of as little as 10 pg of purified RNA. The method utilizes primer-mediated depletion for effective removal of specific transcripts from RNA-Seq libraries without perturbing the original total RNA population. This results in a significant reduction in rRNA transcripts and high strand specificity even at minimal input levels. Likewise, there is a growing need to perform DNA-Seq from small sample quantities, either from enrichment workflows such as ChIP-Seq or from challenging sample sources such as liquid biopsy. Unique enzymatic approaches and workflow optimization result in a novel DNA-Seq workflow that can be applied to extremely low inputs without loss of library content to unwanted artifacts. Both novel approaches provide a solution for researchers interested in applications using extremely limited input amounts.

3rd Generation Arrays: New Global Screening Array (GSA) and New Methylation EPIC Array

Presenting Author: Per Hoffmann, Life & Brain
Dirk Bartels, Illumina

Agenda:

First 10 min:
GSA: Per Hoffmann, Life & Brain

The Infinium Global Screening Array combines a highly imputation optimized, multi-ethnic genome-wide backbone, hand curated clinical research variants, and sample tracking content to create a high-powered, economical array for population-scale genomics and screening. With over xx million samples sold, the GSA will become the new standard in GWAS.
Be part of this success story and join the European GSA consortium.

Second 10min:
EPIC: Dirk Bartels, Illumina

Being build on the industry-leading Methylation 450k array the EPIC adds additional 350,000 CpGs in enhancer regions derived from ENCODE and FANTOM5. Using the highly robust Infinium workflow the EPIC is suitable for all types of samples including FFPE offering a unique combination of comprehensive, expert selected coverage, high sample throughput and an affordable price.

Third 10 min:
Discussion about coordinated e:Med activities

Sample-to-Insight NGS Solutions for Liquid Biopsy, hereditary disease and cancer clinical testing, microbiome and RNA-sequencing Analysis and Interpretation

Presenting Author: Dr. Anika Joecker, Director, Global Product Management

QIAGEN Bioinformatics

With the acquisition of CLC bio, Ingenuity Systems and Biobase, QIAGEN became a global leader in the development and delivery of commercial-grade, enterprise bioinformatics software solutions for implementation of genomics in research and clinical applications. Our extensive experience of more than 16 years allows genomics testing laboratories to adopt NGS capabilities and achieve efficiencies across the discovery-to-testing continuum. Our software solutions, which include data analysis, data interpretation and reporting, have been designed to support genomics laboratories in efficiently scaling test volume, data, and menus across a broad range of NGS applications and platforms. The solutions are powered by QIAGEN's industry-leading, proprietary, and continually curated Knowledge Base, enabling laboratories to filter, interpret and report test results with an up-to-date and vast source of scientific and clinical information.
In this presentation we will mainly focus on our new sample to insight solutions for RNA-seq biomarker discovery, microbiome applications, ccfDNA cancer liquid biopsy and hereditary disease/oncology clinical testing.

Poster Presentations

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

Poster Session I
Poster Flash Talks I, October 5, 11:00 – 11:30 am
Poster Exhibition I, October 5, 11:30 – 12:30 pm
Cross topic issues I - Disease Manifestation
Specific Diseases I - Infection & Inflammation
Cross topic issues II - Heterogeneity of Disease

Poster Session II
Poster Flash Talks II, October 5, 05:40 – 06:10 pm
Poster Exhibition II, October 5, 06:10 – 07:00 pm
Specific Diseases II – Neuropsychiatric Disorders
Cross topic issues III – Therapy Response Prediction
ELSA of Systems Medicine

Page	Abstract	Presenting Author	Poster Title	e:Med associations
Cross-topic issues I: Disease Manifestation				
113	P - CT I - 1, FT	Manuel Gunkel	Automated targeted 3D imaging of tissue microarrays for telomere analysis in prostate cancer	CancerTelSys
114	P - CT I - 2	Wolfram Gronwald	Novel insights into glutamine usage of activated B-lymphocytes	MMML-Demonstrators
115	P - CT I - 3	So-Young Lim	KDM1A confers invasive and metastatic attributes in lung adenocarcinoma by modulating a non-canonical Integrin ß3-KRAS signaling axis	SMOOSE
116	P - CT I - 4	Xiaojie Yu	The tumor suppressor microRNA is transported extracellularly in liver cancer cells	SMOOSE
117	P - CT I - 6, FT	Daniela Esser	Cross-disease analyses reveal common transcriptomic signatures of inflammatory phenotypes	SysINFLAME
118	P - CT I - 7	Anita Bhandari	Functional evaluation of the coronary artery disease risk gene ADAMTS-7 in Drosophila melanogaster	e:AtheroSysmed
119	P - CT I - 8, FT	Matthias Munz	A 1,000 Genomes Phase3-based genome-wide association meta-analysis of coronary artery disease and periodontitis	e:AtheroSysmed
120	P - CT I - 9, FT	Hagen Klett	Spatio-Temporal organization of coding and non-coding RNA in zebrafish heart regeneration	DeCaRe
121	P - CT I - 10	Ashraf Yusuf Rangrez	Myeloid Leukemia Factor 1 is a Stress Responsive Modulator of Neonatal Rat Cardiomyocyte Proliferation	SYMBOL-HF
122	P - CT I - 11	Phillip Hoppe	miR-301 Regulates Cofilin-2 in Calsarcin-1 deficient mice, a mouse model of dilated cardiomyopathy	
123	P - CT I - 12	Annika Kluge	Rnd1: A Novel Stretch-Responsive Gene Induces Cardiac Hypertrophy and Proliferation	
Specific diseases I: Infection & Inflammation				
127	P - SD I - 1	Peter Ahnert	Visual Exploration of Cross-Sectional Data	CAPSyS
128	P - SD I - 2	Petra Creutz	CAPSyS Deep Phenotyping Study	CAPSyS
129	P - SD I - 3, FT	Holger Kirsten	Gene expression patterns in blood predict the time course of community acquired pneumonia	CAPSyS
130	P - SD I - 4	Bernd Schmeck	Macrophages render alveolar epithelial cells hypo-responsive to Legionella pneumophila – a combined experimental and in silico study	CAPSyS
131	P - SD I - 5	Arturo Blázquez Navarro	BKV and CMV coinfection in renal transplant patients: results from a large multicenter study	e:Kid
132	P - SD I - 6, FT	Nadine S. Schaadt	A systems medicine approach to define clinically relevant immune cell infiltrations in biopsies of transplanted kidneys	SYSIMIT
133	P - SD I - 7	Dr. Juan Carlos Lopez Alfonso	In-silico insights on the prognostic potential of immune cell infiltration patterns in the breast lobular epithelium	SYSIMIT
134	P - SD I - 8	Jörn Weisner	Identification and Characterization of Novel Small Molecule Nrf2 Modulators	SMOOSE

Poster Flash Talk marked by FT

Page	Abstract	Presenting Author	Poster Title	e:Med associations
Specific diseases I: Infection & Inflammation				
135	P - SD I - 9	Richa Bharti	Role of Atg16l1 in regulating temporal changes in intestinal microbiota during pregnancy	SysINFLAME
136	P - SD I - 10	Abdou Elsharawy	Molecular Profiling and Diagnostic Potential of Extracellular Vesicles in Inflammatory Bowel Disease (IBD) and Colorectal Cancer (CRC)	SysINFLAME
137	P - SD I - 11	Femke-Anouska Heinsen	Gut microbial profiles of German primary sclerosing cholangitis patients in comparison to ulcerative colitis patients and healthy controls	SysINFLAME
138	P - SD I - 12	Carina Kreutzer	Hypothalamic inflammation in human obesity is mediated by environmental and genetic factors and is not reversed by bariatric surgery	SysINFLAME
139	P - SD I - 13	Jacqueline Moltzau Anderson	NOD2 affects microbial resilience after antibiotic treatment in mice	SysINFLAME
140	P - SD I - 14	Elke Rodriguez	Association of atopic dermatitis with cardiometabolic diseases and risk factors	SysINFLAME
141	P - SD I - 15	Elisa Rosati, Marie Dowds	Dynamic changes of the immune repertoire of IBD patients during different biologic therapies	SysINFLAME
142	P - SD I - 16	Ulrich Sax	Integrated Research Data Management System of sysINFLAME	SysINFLAME
143	P - SD I - 17	Go Ito	The role of the Ikba gene family member NFKBIZ in colitis associated cancer	
144	P - SD I - 18	Linda Krause	Genome-Wide Integrative Analysis of T Helper Cells	
Cross-topic issues II: Heterogeneity of Disease				
149	P - CT II - 1, FT	Ulrich Sax, Frank Kramer	MyPathSem: From Data to Pathways	i:DSem – MyPathSem
150	P - CT II - 2, FT	Michael Altenbuchinger	Reference point insensitive molecular data analysis	MMML-Demonstrators
151	P - CT II - 3	Christian Karmen	A Similarity Measure for Clinical Attributes using the Kaplan-Meier Estimator	CLIOMMICS
153	P - CT II - 4	Raik Otto	Robust In-Silico identification of sequenced Cancer Cell Lines	MAPTor-NET
154	P - CT II - 5, FT	Grischa Toedt	SUPR-G: Systems biology of the Unfolded Protein Response in Glioma	SUPR-G
155	P - CT II - 6	Alexandra Poos	Modelling telomere maintenance mechanisms in tumour cells	CancerTelSys
156	P - CT II - 7	Markus Rehm	An approach towards predicting melanoma cell death induced by 2nd generation TRAIL receptor agonist IZI1551 in single and combination treatment with IAP antagonist TL32711/Birinapant	Melanoma sensitivity
157	P - CT II - 8	Kerstin Schönbeck	The Hippo-YAP1-pathway is activated in relapsed and MYCN amplified neuroblastoma	SMOOSE, SYSMED-NB

Poster Flash Talk marked by FT

Page	Abstract	Presenting Author	Poster Title	e:Med associations
Cross-topic issues II: Heterogeneity of Disease				
158	P - CT II - 9	Hansjörg Baurecht	Epidemiologic and genetic association between atopic dermatitis, rheumatoid arthritis, inflammatory bowel disease, and type-1 diabetes	SysINFLAME
159	P - CT II - 10	Britt-Sabina Petersen	Targeted gene panel sequencing for early-onset inflammatory bowel disease	SysINFLAME
161	P - CT II - 11	Kristina Paulsen	Small, dense LDL cholesterol is a cardiovascular risk factor in several chronic inflammatory diseases	SysINFLAME
162	P - CT II - 12, FT	Julia Krause	Long non-coding RNA RP1-79C4.4 as novel candidate gene for atrial fibrillation?	symAtrial
163	P - CT II - 13	Maria Fedorova	LPPdb: a database for integration of structural, functional, biological and clinical information on oxidized lipids based biomarkers	SysMedOs
Specific diseases II: Neuropsychiatric Disorders				
167	P - SD II - 1	Urs Braun	Dynamic reconfiguration of brain networks: links to schizophrenia risk and NMDA receptor function	IntegraMent
169	P - SD II - 2	Jan Deussing	Cross-disorder risk gene CACNA1C differentially modulates susceptibility to psychiatric disorders during development and adulthood	IntegraMent
170	P - SD II - 3	Urs Heilbronner	Common genetic variants associated with personality dimensions in the Heidelberg Cohort Study of the Elderly (HeiDE)	IntegraMent
172	P - SD II - 4	Anna C. Koller	Exome sequencing of 37 multiply affected schizophrenia families provides new insights into the pathogenesis of the disorder	IntegraMent
173	P - SD II - 5	Gaurav Jain	Therapeutic Targets for Individualized Therapy of Schizophrenia Patients	IntegraMent
174	P - SD II - 6	Sergi Papiol	Enrichment of genetic variants associated with clinical response to lithium in circadian clock system gene sets	IntegraMent
175	P - SD II - 7	Janina Schweiger	BDNF genotype modulates connectivity during cognitive control in humans	IntegraMent
176	P - SD II - 8	Sandra van der Auwera	The inverse link between genetic risk for schizophrenia and migraine through NMDA (N-methyl-D-aspartate) receptor activation via D-serine	IntegraMent
177	P - SD II - 9	Stephanie Witt	Genome-wide association study of Borderline Personality Disorder reveals genetic overlap with Bipolar Disorder and Schizophrenia	IntegraMent
179	P - SD II - 10	Karolina Worf	Network-based stratification of schizophrenia patients using rare variants	IntegraMent
180	P - SD II - 11	Jens Treutlein	Association between Neuropeptide Y Receptor Y2 (NPY2R) Promoter Variant rs6857715 and Major Depressive Disorder	IntegraMent, SysMedAlcoholism

Poster Flash Talk marked by FT

Page	Abstract	Presenting Author	Poster Title	e:Med associations
Specific diseases II: Neuropsychiatric Disorders				
181	P - SD II - 12	Gaby Schneider	A stochastic model relates responses to bistable stimuli to underlying neuronal processes	PsychoSys
182	P - SD II - 13	Katrin Charlet	Influence of habitual negative affect on processing of negative facial stimuli in alcoholic patients	SysMedAlcoholism
183	P - SD II - 14, FT	Josef Frank	Analysis of tissue specific genetically determined fraction of gene expression in alcohol dependent patients	SysMedAlcoholism
184	P - SD II - 15	Patrick Schloss	Generation and neuronal differentiation of induced pluripotent stem cells from „humanized“ mice carrying the respective human OPRM1 A118G alleles	SysMedAlcoholism
185	P - SD II - 16	Fanny Aldinger	Polygenic burden analysis of longitudinal clusters of quality of life and functioning in patients with severe mental illness	
187	P - SD II - 17, FT	Janos Kalman	Using machine learning to build individualized prediction models of future Quality of Life in psychosis patients	
ELSA of Systems Medicine				
191	P - ELSA - 1	Sebastian Schleidgen	Patient Participation in Systems Medicine	ELSA DASYMED
192	P - ELSA - 2	Katharina Viktoria Röntgen	Trust matters – Ethical Reasons for better Availability of Guidelines and Policies about Acquiring, Storing and Processing Epigenetic Data in Systems Medicine	ELSA EDEA
193	P - ELSA - 3	Ulrich Sax	GenoPerspektiv: Infrastructure, Ethical, Legal and Social Aspects of High Throughput Analyses in the Clinic	ELSA GenoPerspektiv
194	P - ELSA - 4, FT	Regine Kollek	What does ‘translation’ mean in systems medicine?	ELSA ModMed
195	P - ELSA - 5	Friedhelm Meier	SYSKON. Re-Configuration of Health and Disease. Ethical, Psycho-Social, Legal and Health-Economic Challenges of Systems Medicine: The Case of Hereditary Breast Cancer.	ELSA SYSKON
Cross-topic issues III: Therapy Response Prediction				
199	P - CT III - 1	Meike Kasten	Proof of concept clinical trial	Mito-PD
200	P - CT III - 2	Valentina Vengeliene	The alcohol deprivation effect model for studying relapse behaviour	SysMedAlcoholism
201	P - CT III - 3	Ateequr Rehman	Biological therapies and intestinal microbiota: A longitudinal study in diverse disease phenotype	SysINFLAME
202	P - CT III - 4	Johannes Zimmermann	Community-level modeling of gut microbial interactions in short chain fatty acid metabolism	SysINFLAME
203	P - CT III - 5	Markus Scholz	Modeling individual time courses of thrombopoiesis during multi-cyclic chemotherapy	HaematoOPT

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Page	Abstract	Presenting Author	Poster Title	e:Med associations
Cross-topic issues III: Therapy Response Prediction				
204	P - CT III - 6	Markus Scholz	A tool for guided therapy adaptation to control for haematotoxic side-effects of multicycle chemotherapy	HaematoOPT
205	P - CT III - 7, FT	Markus Scholz	Model-based optimization of G-CSF treatment	HaematoOPT
206	P - CT III - 8	Harald Seitz	Anti-HLA antibody signatures provide a new tool for early diagnostics of acute graft rejection after renal transplantation	e:Kid
207	P - CT III - 9, FT	Ralf Schönmeyer	Discovery of novel biomarkers based on spatial immune cell patterns	SYSIMIT
208	P - CT III - 10, FT	Stefan Wiemann	HER2Low – Targeting the ERBB-module in HER2-low breast cancer	HER2Low
209	P - CT III - 11	Slim Khouja	Dissecting MAPK/mTOR-associated Drug Sensitivity Using a Genome-Wide CRISPR Synthetic Lethality Screen in Pancreatic Neuroendocrine Tumors	MAPTor-NET
210	P - CT III - 12	Dagmar Kulms	Mechanistic insight into the consequences of sublethal drug doses on therapeutic responses and unwanted metastatic outgrowth of malignant melanoma	Melanoma sensitivity
211	P - CT III - 13, FT	Philippe Lucarelli	FALCON: A Fast Algorithm for the Contextualisation of Logical Network Models	Melanoma sensitivity
212	P - CT III - 14	Christian Praetorius	Compounds triggering ER stress-induced cell death in NRASmut melanoma - Can response be predicted?	Melanoma sensitivity
213	P - CT III - 15	Martin Siegemund	Fusion proteins with hexavalent TRAIL assembly for melanoma therapy	Melanoma sensitivity
214	P - CT III - 16	Erhan Kenar	Integrating data, tools and infrastructure to enable efficient collaboration and management in the MultiscaleHCC consortium	Multiscale HCC
215	P - CT III - 17	Frank Kramer	Boosting Therapy Response Prediction via the efficient Re-use and Integration of available Pathway Knowledge for Patient Stratification	MultiPath, i:DSem MyPathSem
216	P - CT III - 18, FT	Iris Macheleidt	LSD1 inhibitor HCI-2509 reduces tumor growth in vitro and in vivo – implications for a novel therapy in NSCLC?	SMOOSE
217	P - CT III - 19, FT	Marco Lodrini	Network analysis of epigenetically controlled microRNAs in neuroblastoma	SYSMED-NB
218	P - CT III - 20	Alexander Schramm	Primary sugar metabolism: an Achilles heel of MYCN-dependent tumors?	SYSMED-NB
219	P - CT III - 21, FT	Birgit Luber, Dieter Maier	Identification of predictive response and resistance factors to targeted therapy in gastric cancer using a systems medicine approach	SYS-Stomach
220	P - CT III - 22	Adriana Pitea	Deliniating multi-omics networks of radiation sensitivity in head and neck squamous cell carcinoma.	
221	P - CT III - 23	Jaber Dehghany	The role of cell migration in cancer and transplantation	SYS-Stomach

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Poster Flash Talks

Poster Session I
Poster Flash Talks I, October 5, 11:00 – 11:30 am
Cross topic issues I - Disease Manifestation
Specific Diseases I - Infection & Inflammation
Cross topic issues II - Heterogeneity of Disease

Poster Session II
Poster Flash Talks II, October 5, 05:40 – 06:10 pm
Specific Diseases II – Neuropsychiatric Disorders
Cross topic issues III – Therapy Response Prediction
ELSA in Systems Medicine

Poster Flash Talks I
October 5, 11:00 – 11:30 am

Page	Abstract	Presenting Author	Poster Title	e:Med associations
Cross-topic issues I: Disease Manifestation				
113	P - CT I - 1, FT	Manuel Gunkel	Automated targeted 3D imaging of tissue microarrays for telomere analysis in prostate cancer	CancerTelSys
117	P - CT I - 6, FT	Daniela Esser	Cross-disease analyses reveal common transcriptomic signatures of inflammatory phenotypes	SysINFLAME
119	P - CT I - 8, FT	Matthias Munz	A 1,000 Genomes Phase3-based genome-wide association meta-analysis of coronary artery disease and periodontitis	e:AtheroSysmed
120	P - CT I - 9, FT	Hagen Klett	Spatio-Temporal organization of coding and non-coding RNA in zebrafish heart regeneration	DeCaRe
Specific diseases I: Infection & Inflammation				
129	P - SD I - 3, FT	Holger Kirsten	Gene expression patterns in blood predict the time course of community acquired pneumonia	CAPSyS
132	P - SD I - 6, FT	Nadine Schaadt	A systems medicine approach to define clinically relevant immune cell infiltrations in biopsies of transplanted kidneys	SYSIMIT
Cross-topic issues II: Heterogeneity of Disease				
149	P - CT II - 1, FT	Ulrich Sax, Frank Kramer	MyPathSem: From Data to Pathways	i:DSem – myPathSem
150	P - CT II - 2, FT	Michael Altenbuchinger	Reference point insensitive molecular data analysis	MMML-Demonstrators
154	P - CT II - 5, FT	Grischa Toedt	SUPR-G: Systems biology of the Unfolded Protein Response in Glioma	SUPR-G
162	P - CT II - 12, FT	Julia Krause	Long non-coding RNA RP1-79C4.4 as novel candidate gene for atrial fibrillation?	symAtrial

Poster Flash Talks II
October 5, 05:40 – 06:10 pm

Page	Abstract	Presenting Author	Poster Title	e:Med associations
Specific diseases II: Neuropsychiatric Disorders				
183	P - SD II - 14, FT	Josef Frank	Analysis of tissue specific genetically determined fraction of gene expression in alcohol dependent patients	SysMedAlcoholism
187	P - SD II - 17, FT	Janos Kalman	Using machine learning to build individualized prediction models of future Quality of Life in psychosis patients	
ELSA in Systems Medicine				
194	P - ELSA - 4, FT	Regine Kollek	What does 'translation' mean in systems medicine?	ELSA ModMed
Cross-topic issues III: Therapy Response Prediction				
205	P - CT III - 7, FT	Markus Scholz	Model-based optimization of G-CSF treatment	HaematoOPT
207	P - CT III - 9, FT	Ralf Schönmeyer	Discovery of novel biomarkers based on spatial immune cell patterns	SYSIMIT
208	P - CT III - 10, FT	Stefan Wiemann	HER2Low – Targeting the ERBB-module in HER2-low breast cancer	HER2Low
211	P - CT III - 13, FT	Philippe Lucarelli	FALCON: A Fast Algorithm for the Contextualisation of Logical Network Models	Melanoma sensitivity
216	P - CT III - 18, FT	Iris Macheleidt	LSD1 inhibitor HCI-2509 reduces tumor growth in vitro and in vivo – implications for a novel therapy in NSCLC?	SMOOSE
217	P - CT III - 19, FT	Marco Lodrini	Network analysis of epigenetically controlled microRNAs in neuroblastoma	SYSMED-NB
219	P - CT III - 21, FT	Birgit Luber, Dieter Maier	Identification of predictive response and resistance factors to targeted therapy in gastric cancer using a systems medicine approach	SYS-Stomach

e:Med
SYSTEMS MEDICINE

Poster Presentations

Cross-topic Issues I - Disease Manifestation

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

CancerTelSys

Presenting Author: Manuel Gunkel

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

1 VIROQUANT CellNetworks RNAi Screening Facility, Bioquant Center, University of Heidelberg 2 Research Group Genome Organization & Function, German Cancer Research Center (DKFZ) and Bioquant Center 3 Department of Bioinformatics and Functional Genomics, Biomedical Computer Vision Group, Bioquant Center and IPMB, University of Heidelberg and German Cancer Research Center (DKFZ) 4 Department of Pathology, University Medical Center Hamburg-Eppendorf

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

Novel insights into glutamine usage of activated B-lymphocytes

MMML-Demonstrators

Presenting Author: Wolfram Gronwald

Maren Feist(1), Philipp Schwarzfischer(2), Paul Heinrich(2), Katja Dettmer(2), Wolfram Gronwald(2), Peter J. Oefner(2), Dieter Kube(1)

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Activated and transformed lymphocytes undergo similar metabolic reprogramming to support proliferation. In this process both cells increase glucose and glutamine consumption. Glucose is metabolized via glycolysis to lactate to produce energy and building blocks for cell proliferation. It is long known that glutamine is important/critical for lymphocyte proliferation. However, the fate of glutamine in lymphocytes is complex and not fully understood yet. The main regulator of metabolism in lymphocytes/cancer is the oncogene Myc, which regulates among others glucose independent TCA, proline synthesis from glutamine, nucleotide synthesis and glutathione synthesis. While T lymphocytes are frequently investigated, less is known about B lymphocytes. It is often assumed that they are similar, but recent results point at distinct differences. So far, most studies have concentrated on Myc regulated metabolism in lymphocytes (see above), but metabolism can also be changed by microenvironmental factors (BAFF) and other pathways such as ERK/MAP. As a consequence we address the following questions: Do B cells, activated by the microenvironment or by oncogenic mutations, rely on equal changes in glutamine metabolism to support proliferation? Do distinct types of lymphoma, which rely on different pathway activations, differ in glutamine usage to support proliferation? Which key players are involved in these metabolic adaptations? Results of this study may lead to more specific targets for cancer therapy without affecting normal immune function.

KDM1A confers invasive and metastatic attributes in lung adenocarcinoma by modulating a non-canonical Integrin ß3-KRAS signaling axis

SMOOSE

Presenting Author: So-Young Lim

So-Young Lim1,3, Iris Macheleidt1,3, Stephan Schäfer1, Luca Ozretic1, Sabine Merkelbach-bruse1, Jürgen Wolf2, Roman Thomas4, Michal Schweiger5, Margarete Odenthal1,2, and Reinhard Büttner1,2

1Institut of Pathology, University Hospital of Cologne, 2Clinic for internal medicine, University Hospital of Cologne, Kerpener Strasse 62, 50294 Cologne, Germany, 3The Center for Molecular Medicine Cologne (CMMC), Robert-Koch-Strasse 21, 50931, Cologne, Germany, 4Department of Translational Genomics, University of Cologne, 5Funtional Epigenomics, Universtiy of Cologne, Weyertal 115b 50931 Cologne, Germany

KRAS mutations occur in approximately 25% of non-small cell lung cancer (NSCLC). They account for the therapy resistance to the EGFR inhibitors and are suggested to be difficult to target by specific drugs. Therefore, new therapies for KRAS mutant NSCLC are urgently needed. The histone H3K4 and H3K9 di/mono-demethylase KDM1A is a key epigenetic writer, aberrantly upregulated in many cancer types, including NSCLC. In order to understand the functional role of KDM1A in the progression of NSCLC, KDM1A expression profiles were analysed in tissue microarrays (TMAs) including 182 lung adenocarcinoma. KDM1A expression correlated with high grade and metastasized tumor. To investigate the impact of KDM1A in NSCLC development, we used the KRAS mutated A549 lung adenocarcinoma cell line to establish a shRNA-mediated stable KDM1A knock-down cell clon. Unexpectedly, KDM1A knock-down had an only slight effect on retardation of cell growth, however, cell invasion and self-renewal capability were significantly decreased by KDM1A inhibition. KDM1A knock-down in A549 cell resulted in a dramatic change in the transcriptome profile as determined by RNA-Seq. Interestingly, genes involved in the KRAS signature were significantly affected upon KDM1A knock-down as revealed by GSEA analysis. Ingenuity pathway analysis also suggested that the alternative integrin ?3-KRAS-NF?B signaling axis, which is involved in stem cell like properties, is abrogated upon KDM1A knock-down. Indeed, Integrin ?3 and its non-canonical ligand galectin-3 were strongly downregulated and their downstream NF?B activity was decreased upon KDM1A knock-down. In conclusion, our findings provide evidence of a KDM1A/KRAS interplay leading to interference of the non-canonical KRAS signal pathway by KDM1A inhibition in NSCLC adenocarcinoma.

The tumor suppressor microRNA is transported extracellularly in liver cancer cells

SMOOSE

Presenting Author: Xiaojie Yu

Xiaojie Yu, Hannah Eischeid, Reinhard Büttner, and Margarete Odenthal

Institute of Pathology, University Hospital of Cologne, Germany

Background and Aim: miR-198 has been proven as a tumor suppressor in different cancer types, inhibiting cell growth and proliferation. Previous studies have shown that miR-198 is the most downregulated miRNA during liver diseases progression. Therefore we aimed to study the regulation of miR-198 in liver cancer cells. Methods: miR-198 expression cassette was cloned under doxycycline induced tet-on promoter and stably transfected into liver cancer cells. RNA was isolated and real time PCR was performed to analyze miR-198 expression level. As well, the supernatants were collected and after serial centrifugation the exosomes were precipitated. The isolated exosomes were further characterized by Western Blotting and real time PCR. Exosomal proteins were analyzed using mass spectrometry. MicroRNA PCR array was made to identify exosomal microRNAs. Immunoprecipitation method was used to identify miR-198 associated proteins. Furthermore, cell viability assay was performed to study the effect of conditioned media collected from miR-198 overexpressing cells. Results: Intracellular miR-198 level was at first strikingly upregulated after doxycycline treatment, which was followed by significantly decrease. Interestingly, the level of extracellular miR-198 was massively upregulated in a time dependent manner. Exosomes, isolated from supernatant of miR198 overexpressing cells, were identified with marker proteins, CD63 and HSP70. Exosomal miR-198 level corresponded with that in the supernatant. Conditioned media, containing exosomes from miR-198 overexpressing cells, strikingly inhibited proliferation of cell types which have no endogenous miR-198. Conclusion: In liver cancer cells, intracellular miR-198 is tightly controlled and is preferably sequestered in vesicles and secreted via exosomes, which might explain why most tumor suppressor microRNAs are downregulated in liver cancer cells. Further experiments would rely on miR-198 anti-sense conjugated nanoparticles to unravel the miRNA sorting mechanisms.

Cross-disease analyses reveal common transcriptomic signatures of inflammatory phenotypes

SysINFLAME

Presenting Author: Daniela Esser

Daniela Esser, Peer Aramillo Irizar, Christoph Kaleta

Institute for Experimental Medicine, UKSH Kiel

Chronic inflammatory disorders are complex diseases, whose precise etiology remains unknown in most cases. Affected patients have a greater risk of developing a further chronic inflammatory disease than population controls. Genome-wide association studies demonstrated already a considerable overlap in their common genetic susceptibility. However, little is known about conserved transcriptomic changes, although these could reveal insights into environmental causes as well as molecular factors. In our study we determined common as well as disease-specific regulatory signatures across seven chronic inflammatory diseases (Ulcerative colitis, Crohn's disease, Psoriasis, Coronary artery disease, Periodontitis, Sarcoidosis, Chronic obstructive pulmonary disease) covering over 4000 samples. Thereby, a conserved core inflammatory molecular signature was identified, which is a step toward understanding processes underlying comorbidity. This further enables to predict the effect of a treatment with novel drugs or drugs already known from another disease. Additionally, we could identify disease-specific patterns allowing for a more precise distinction between the investigated inflammatory diseases. Additionally, chronic inflammation is associated with further disease-phenotypes such as cancer and aging. Therefore, we compared the inflammatory signature with samples derived from three tissues from old and young healthy individuals as well as with transcriptomic patterns of 14 distinct cancer types. Thereby, we could show that while the inflammatory signature promotes cancer, it is surprisingly opposing aging-associated changes. In summary, the identification of a transcriptomic signature of inflammation across different inflammatory phenotypes is a key step toward understanding the etiology of chronic inflammatory diseases, their association with cancer as well as aging-associated diseases and will help to detect novel drugs and treatment approaches.

Functional evaluation of the coronary artery disease risk gene ADAMTS-7 in Drosophila melanogaster

e:AtheroSysmed

Presenting Author: Anita Bhandari

Anita Bhandari and Jeanette Erdmann

Institute for Integrative and Experimental Genomics, University of Lübeck; DZHK (German Research Centre for Cardiovascular Research) and University Heart Center Luebeck

Coronary artery disease (CAD) is a complex disorder resulting from an interplay of lifestyle and genetic factors. Among these lifestyle factors, cigarette smoking is one of the strongest risk factors. Genome-wide association studies (GWASs) indicated that gene-smoking interactions in CAD are in part mediated by the CAD-risk gene ADAMTS-7. Particularly, allelic variation at rs7178051 that associates with reduced ADAMTS-7 expression conferred stronger CAD protection in “never-smokers” compared to “ever-smokers”. The loss of CAD protection is likely due to induction of ADAMTS-7 expression in the vasculature by cigarette smoking. ADAMTS-7 is a member of the “a disintegrin and metalloproteinase with thrombospondin motifs” (ADAMTS) family, which plays a crucial role in neo-intima formation and vessel stenosis. Thus, a detailed understanding of the ADAMTS-7 CAD risk gene is of significant importance. We studied previously smoking exposure in Drosophila. Interestingly our RNA-seq analysis results revealed high expression of the ADAMTS-7 homolog CG4096 in the tracheas of smoke-exposed flies, indicating that it might play an important role in this gene-smoking in-teraction. Therefore our main objective is to unravel the physiological role and function of ADAMTS-7 in Drosophila melanogaster and specifically to understand the interconnection between cigarette-smoking and the CAD-risk variants at the ADAMTS-7 risk locus observed in humans. The fruit fly consists of a primitive vascular system in comparison to other inver-tebrate models and the molecular mechanisms that regulate the formation of the tracheal tube seem to be similar to those that are involved in shaping the vascular tube in mammals. This made Drosophila to the most informative invertebrate model for studying the genesis of tubular organs such as the lung or the kidney and at the same time for complex processes such as angiogenesis. Herein, we introduce the establishment of a novel Drosophila model to study the role of ADAMTS-7 and its interaction with cigarette smoke.

A 1,000 Genomes Phase3-based genome-wide association meta-analysis of coronary artery disease and periodontitis

e:AtheroSysmed

Presenting Author: Matthias Munz

Matthias Munz1,2,3, Henrik Dommisch2, Arne Schäfer2,3, Jeanette Erdmann1

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Strong evidence of associations between the presence of coronary artery disease (CAD) and the oral inflammatory disease periodontitis (PD) is derived from multiple randomized clinical trials and shows that the epidemiological association between both diseases is independent of the shared risk factor smoking. Yet, at the time being, a causative relationship between CVD and PD is not being supported by clear experimental evidence. Recently, various studies demonstrated that the CAD associations of GWAS-lead SNPs at the genes ANRIL and PLASMINOGEN (PLG) are shared with PD. Additionally, a shared association of a rare intronic variant within the gene CAMTA1 was reported. To further elucidate the genetic basis of PD and CAD, we will perform a meta-analysis with the worldwide largest sample of aggressive periodontitis (AgP; N= 896 cases, N= 7,090 controls) and the German Myocardial Infarction Family Studies 1-5 (GerMIFs1-5; N= 3,991 cases, N= 5,510 controls). The AgP case-control sample of German (AgP-Ger) and Dutch (AgP-NL) descent was genotyped using Illumina OmniExpress BeadChips. The GerMIFs1-5 were genotyped using Affymetrix Mapping 500K Array (GerMIFs1) and Affymetrix Genome-Wide Human SNP Array (GerMIFs2-5). All genotypes were imputed (1000G Phase3 EUR haplotype reference), followed by a separate analysis (allelic model; adjusted for covariates sex, smoking [AgP] and sex, age, bmi [GerMIFs1-5]). Subsequently, a meta-analysis will be applied on the GWAS results (random effects model) with additional filtering (pmeta < pAgP-Ger, pAgP-NL, pGerMIFs1, pGerMIFs2, pGerMIFs3, pGerMIFs4, pGerMIFs5; pmeta < 0.05 for LD SNPs with r2 > 0.8 [linkage disequilibrium]). Genome-wide significant SNP associations will be replicated in silico in a second GWAS sample of the more moderate but widespread form chronic PD, and will be functionally analyzed in silico for expression quantitative trait loci effects. The knowledge of the potential shared genetic basis of CAD and PD will improve the understanding of shared molecular disease mechanisms and will contribute significant data to the current discussion on a causative relationship between CVD and PD.

Spatio-Temporal organization of coding and non-coding RNA in zebrafish heart regeneration

DeCaRe

Presenting Author: Hagen Klett

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

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

The human heart has a very limited capability to regenerate after injury. Therefore, loss of cardiomyocytes, e.g., due to myocardial infarction, often results in heart failure and death. On the other hand, zebrafish are an established in vivo model to study cardiac regeneration. However, the underlying mechanisms are still unclear. Elucidating the capability of cardiac regeneration would lead by similarity to improved therapeutic interventions in humans. To obtain a holistic overview on the transcriptional processes during cardiac regeneration in zebrafish, we analyzed mRNA and miRNA of whole hearts at days 1, 4, 7, 14, 21, 30, 45, 60, 120, 160, post cryoinjury. Functional analysis revealed both transient and persistent processes over time. By comparison to a spatially resolved transcriptome analysis as well as longitudinal echocardiography and lateral brightfield images post cryoinjury we linked the temporal responses to injury area, border zone and uninjured myocardium. Cell cycle, inflammation and regeneration processes peak between days 4 and 7 and decrease slowly to sham levels until day 45. This response could be tied to the injury area of the heart that also decreased in size and was lastly detectable at day 30. To elucidate the role of miRNAs during heart regeneration we used elastic net regularization to predict miRNA-mRNA interactions from transcriptome expression data. From the inferred interaction network we identified several miRNAs important in cardiac regeneration. Deciphering of the transcriptome data revealed how heart regeneration follows a well-orchestrated pattern of time-sequential pathway activation and allows the identification of important key players. As part of the DeCaRe initiative, key players will be further validated by perturbation experiments and integrated with methylome data.

Myeloid Leukemia Factor 1 is a Stress Responsive Modulator of Neonatal Rat Cardiomyocyte Proliferation

SYMBOL-HF

Presenting Author: Ashraf Yusuf Rangrez

Ashraf Yusuf Rangrez1,2, Jost Pott1, Annika Kluge1, Robert Frauen3, Katharina Stiebeling1, Samuel Sossalla1,2, Norbert Frey1,2, Derk Frank1,2

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Myeloid leukemia factor 1 (MLF1) encodes an oncoprotein which is known to play a role in the phenotypic determination of hemopoetic cells. In present study, MLF1 was significantly downregulated after induction of biomechanical stress by phasic biaxial stretch in neonatal rat cardiomyocytes. Consistently, MLF1 was profoundly downregulated in in vivo mouse models of cardiac hypertrophy and cardiomyopathy, and also significantly reduced in human patients of dilated cardiomyopathy, both at transcript and protein levels. MLF1 exhibited pleiotropic effects in cardiomyocytes as its overexpression suppressed hypertrophic growth and cell proliferation while augmenting apoptosis. As expected, knockdown of MLF1 protected cardiomyocytes from apoptosis and accentuated cell proliferation. The apoptosis induction in cardiomyocytes due to MLF1 is attributed to the increased activation of caspase-3/-7/PARP-dependent apoptotic signaling and upregulation of p53. Most interestingly, MLF1 knockdown upregulated the expression of D cyclins significantly, suggesting its direct role in cyclin-dependent cell proliferation. Taken together, our data presents a first line of evidence and suggests an important role MLF1 plays in cardiomyocyte proliferation. These proliferative effects MLF1 exerted on neonatal cardiomyocytes are of particular importance considering the fact that postnatal cardiomyocytes are terminally differentiated. Further in vivo experimental validations are needed to extend the potential therapeutic usage of MLF1 to combat cell degeneration in cardiomyopathy conditions.

miR-301 Regulates Cofilin-2 in Calsarcin-1 deficient mice, a mouse model of dilated cardiomyopathy

Presenting Author: Phillip Hoppe

Phillip Hoppe1, Elisa Zille1, Ashraf Rangrez1,2, Alexander Bernt1,2, Norbert Frey1,2, Derk Frank1,2

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Dilated cardiomyopathy (DCM) is a major cause for heart failure and a causative genetic background is suspected in up to 50% of all DCM cases. The underlying molecular pathways though remain poorly understood. Calsarcin-1 deficient (CS1ko) mice display DCM phenotype and were used in this study to identify differentially regulated microRNAs for their potential role in disease phenotype. These mice showed upregulation of fetal genes (e.g., Nppa, Nppb) and the calcineurin dependent gene Rcan1.4. Interestingly, no signs of hypertrophy or fibrosis were detected in these mice. A Microarray screening experiment revealed dysregulation of several microRNAs such as miR-301a, miR-362 and miR29b were highly downregulated, whereas, miR-679, miR-296, miR-298 were significantly upregulated. Further characterization resulted in identification of Cofilin-2 (Cfl2), an actin depolymerization factor of the ADF/Cofilin family, as a target of miR-301a via luciferase assay which was further confirmed by mutating predicted binding sites. Additionally, Cfl2 is found to be upregulated in CS1ko where miR-301 is reduced. Along the same lines, overexpression of miR-301a reduced, while its knockdown upregulated the Cfl2 expression in neonatal rat ventricular cardiomyocytes (NRVCM). Similarly, expression of fetal genes was conversely related to the expression of miR-301, though it did not affect cell surface area. Taken together, our data show Cfl2 as a target of miR-301a and imply a role for Cfl2 in the pathogenesis of DCM. Cs-1ko mice show a dilated phenotype, strong upregulation of the fetal gene program without a change in cell size which correlates with the findings from miR-301 knockdown or overexpression of Cfl2 in NRVCM. Further in vivo characterization of miR-301 and Cfl2 interactions is proposed to reveal their direct/indirect involvement in DCM which could be exploited further for clinical implications.

Rnd1: A Novel Stretch-Responsive Gene Induces Cardiac Hypertrophy and Proliferation

Presenting Author: Annika Kluge

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1 Department of Internal Medicine III, Cardiology and Angiology, University Medical Center Schleswig-Holstein, Kiel, Germany 2 German Centre for cardiovascular Research, Partner Site Hamburg, Lübeck, Kiel, Germany

Cardiac remodeling is induced by mechanical or humoral stress and leads to several pathological changes of the heart. Understanding the involved mechanisms is critical for the development of potential therapies. After a screening experiment of stretched neonatal rat ventricular cardiomyocytes (NRVCMs) we focused on differentially regulated genes. Interestingly, the upregulated gene coding for Rho family GTPase 1 has not been implicated in the context of cardiac hypertrophy before. In further analyzes we found consistent upregulation of Rnd1 after 24h dynamic stretch (5.94x), stimulation with phenylephrine (PE) (3.98x) and in an in vivo model of mice treated with transverse aortic constriction (2.1x). Adenoviral overexpression of Rnd1 in NRVCM induced the fetal gene program (e.g. nppa, nppb) and a significant increase in cell size was found. Consistent findings are shown after stretch or PE-stimulation. Next, we examined the role of Rnd1 on cell cycle progression using the proliferation markers Ki67 and phosphohistone H3. Rnd1 overexpression showed an increase in Ki67+ cells of about 6.9 fold and in PHH3+ cells of 5.25 fold. After performing an Y2H-screen we identified Myozap as novel interaction partner and confirmed their interaction by several Co-IPs. Because Myozap is known as activator of the SRF-signaling pathways, effects of Rnd1 were determined on SRF-luciferase activity in NRVCMs. As expected, we identified a strong activation of SRF-signaling by Rnd1 overexpression (5.82x). In summary, we could identify a novel stretch-sensitive gene which influences the process of cardiac hypertrophy and cell proliferation. Moreover, we were able to validate Rnd1 as a new binding partner of Myozap and its essential role in the SRF signaling pathway. Current work focuses on knockdown of Rnd1 in an in vivo model to complete its characterization.

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Poster Presentations

Specific Diseases I - Infection & Inflammation

Visual Exploration of Cross-Sectional Data

CAPSyS

Presenting Author: Peter Ahnert

Peter Ahnert (1), Shenghui Cheng (2), Fabian Schwarzenberger (3), Markus Scholz (1), Klaus Müller (2), Markus Löffler (1)

(1) Universität Leipzig, Institut für Medizinische Informatik, Statistik und Epidemiologie (IMISE) (2) Stony Brook University, Center for Visual Computing (3) Hochschule für Technik und Wirtschaft Dresden, Fakultät Informatik/Mathematik

In many clinical and epidemiological studies, valuable data are collected with often substantial human and financial effort. Selection of assessments in such studies is based on current knowledge in the subject field and often aims at investigating specific hypotheses. However, often there is a significant exploratory aspect – data are collected beyond specific hypotheses to enable identification of hitherto unknown correlations and patterns of medical and scientific relevance. Detailed hypotheses based on current knowledge, providing relevant data in a usable form, statistical testing of hypotheses, and validation and interpretation of results, lead to new knowledge and new hypotheses. In this cycle, broad involvement of biomedical specialists who are not always data scientists can be a formidable bottleneck. Enabling these experts to creatively generate many new ideas, some of which solidify into testable hypotheses, could be greatly enhanced by tools allowing intuitively and interactive exploration and visual analysis. The latter makes use of the exceptional image processing and pattern recognition capabilities of humans in conjunction with their expert subject knowledge. Our prototype “Cross Sectional Data Browser” comprises concurrent loading of processed multidimensional numerical and categorical data, presentation of numerical variables in parallel coordinates, presentation of categorical variables in stacked bar charts, clustering, interactive variable selection for cluster analysis and visualization, and visualization of patient similarity distributions. Capabilities are illustrated for data from a study of hospitalized patients with community acquired pneumonia. We plan to complement our prototype “Cross Sectional Data Browser” with a “Longitudinal Data Browser”.

CAPSyS Deep Phenotyping Study

CAPSyS

Presenting Author: Petra Creutz

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Community acquired pneumonia (CAP) is the most common cause of sepsis and death due to infectious diseases. Despite adequate initial antibiotic therapy immunocompetent patients may become critically ill: From local infection of the lung complications from systemic infection to lung failure may arise. Reasons likely involve inadequate host response. As integral part of the systems medicine project “CAPSyS” a deep phenotyping patient study was initialized. Critically ill patients of the PROGRESS-Study (Pneumonia Research Network on Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis) are subjected to in-depth assessment of the lung compartment to investigate innate immune and systemic inflammatory response and the development of a pulmonary endothelial hyperpermeability and lung failure. Assessments include comprehensive clinical monitoring and measurement of extravascular lung water. Blood and airway materials are collected for serial analyses of proteome, metabolome, transcriptome, and microbiome. We aim to recruit 100 ventilated patients with severe CAP. Established workflows, biobank logistics, and data management of the PROGRESS study are build upon. Currently, eight ICUs are recruiting patients (Charité university medicine, Berlin, Vivantes Klinikum Humboldt, Berlin). Additional study centers in Germany will be established. Recruitment started at the end of February 2016. An important goal of CAPSyS is a broader understanding of the pathogenesis of pulmonary infection and alveolo-capillary barrier dysfunction in severe CAP. “Deep phenotyping” goes far beyond existing observational studies of CAP (CAPNETZ, PROGRESS) and aims at providing new data and ideas for the systems medicine approach in CAPSyS, helping to redefine lung disease at a molecular level and providing the basis for discoveries leading to clinical applications for improved diagnostics and interventional strategies.

Gene expression patterns in blood predict the time course of community acquired pneumonia

CAPSyS

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Community acquired pneumonia (CAP) is still an enormous challenge due to its severe manifestations and related costs. Gene-expressions in blood are promising biomarkers to predict disease course and support clinical decision making. Moreover, it provides insights into pathomechanisms of CAP. Within the framework of the PROGRESS study, we followed the disease courses of 394 patients hospitalized with CAP for 28 days including daily assessments of clinical parameters within the first five days. Patient's disease courses differed in severity as measured by the Sepsis-related Organ Failure Assessment (SOFA) score. Death and requirement of intensive care were considered as severe endpoints. Time series of genome-wide gene-expression measurements of whole blood samples were used to predict time courses and endpoints. Analyses are accompanied by comprehensive pathway activation analyses and comparisons with gene-expression patterns observed in related sepsis studies. Our results identified (after multiple-testing-correction) more than 5000 genes related with current disease severity and more than 250 genes associated with current severe endpoints. About 50 genes were associated with future severe endpoints. With increasing severity, pathway analysis showed increased inactivation of many immune-related pathways, especially those of T-cells. Previously proposed expression signatures correlate well with current severity but predict future severity less well. In summary, we found genes and pathways related with present and future CAP-severity that inspire our modelling efforts and can be readily validated in additional cohorts. Our results may help to improve diagnosis, therapy, and outcome for patients with CAP.

Macrophages render alveolar epithelial cells hypo-responsive to Legionella pneumophila – a combined experimental and in silico study

CAPSyS

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Pneumonia is a leading cause of mortality worldwide. To secure organ function, pulmonary innate immune response has to be tightly regulated. Here, we analyses whether macrophages influence immune reactivity of type II alveolar epithelial cells during infection with an intracellular bacterial pathogen.

For this purpose, human macrophage-like differentiated THP-1 cells were co-cultured with human alveolar epithelial A549 cells in a transwell-setting. Infection of THP-1 cells with the important respiratory pathogen Legionella pneumophila (L. pneumophila) resulted in the release of pro-inflammatory cytokines, e.g. IL-8, by co-cultured, non-infected epithelial cells. This effect was synergistically blocked by an IL-1 receptor antagonist (IL-1ra) and a TNF-α neutralizing antibody (anti-TNF-α). Furthermore, co-culture with infected THP-1 cells reduced cytokine expression by epithelial cells following direct encounter with L. pneumophila. This epithelial hypo-responsiveness could be mimicked by stimulation with IL-1β. It was accompanied by an accelerated pro-inflammatory mRNA decay, reduced translocation of transcription factor NF-κB into the nucleus, and less degradation of its inhibitor IκBα. A kinetic mathematical model predicted central involvement of prolonged IRAK-1 degradation in hypo-responsiveness, which could be validated experimentally. IRAK-1-dependent hypo-responsiveness was not mimicked by miR-146a in physiological concentrations or changed by manipulation of histone modifying enzymes.

Our results demonstrate that macrophages can negatively regulate the responsiveness of lung epithelial cells to bacterial infection by the release of IL-1β resulting in a downregulation of IRAK-1. This intercellular communication may be critical for avoiding excessive inflammatory response in the lung.

BKV and CMV coinfection in renal transplant patients: results from a large multicenter study

e:Kid

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BK virus (BKV) and Cytomegalovirus (CMV) reactivations are common health hazards after kidney transplantation (Tx), associated with graft failure and increased morbidity and mortality. It has been postulated that CMV is a risk factor for BKV reactivation, but the effects of a BKV-CMV coinfection remain unknown. To investigate coinfection and its impact on graft function, 3797 blood samples from 541 kidney transplant recipients were analyzed for BKV and CMV load as a part of a large prospective multicenter study. The measurements were performed throughout eight visits during the first post-Tx year. Clinical characteristics, including markers for graft function (GFR), were collected in parallel.

We found that 260 and 91 patients had a detectable BKV and CMV load, respectively. 72% of BKV+ and 87% of CMV+ patients cleared infection one year post-Tx. Infected patients showed an impairment of renal function: in comparison to the rest of population, patients with viral monoinfection (BKV > 2000 copies/mL or CMV > 8000 copies/mL) showed a significant ($P < 0.05$) GFR decline 1-year post-Tx. Additionally, 57 patients were BKV+CMV+; the infections were significantly associated ($P = 0{\cdot}003$). The temporal sequence of the two infections was not uniform: 26 patients showed BKV reactivation before CMV, 19 had CMV before BKV and in 12, both were detected simultaneously. Coinfected patients did not have higher viremias than monoinfected and did not show more rejection episodes. However, even at lower thresholds (BKV > 1000 copies/mL and CMV > 4000 copies/mL) than for monoinfected patients, coinfected patients showed a more pronounced and significant decrease in GFR of 8.5 mL/min 1-year post-Tx ($P < 0.05$) when compared to the rest of the population.

Our results demonstrate the significance of BKV and CMV coinfection for the long-term allograft function and highlight the importance of a good therapeutic monitoring and control of viral reactivations even at low viremia levels.

A systems medicine approach to define clinically relevant immune cell infiltrations in biopsies of transplanted kidneys

SYSIMIT

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Motivation: Renal transplantation induces an adaptive immune response, clinically controlled by immunosuppressive therapy. Protocol biopsies of renal allografts provide important information in addition to clinical markers guiding therapy. Our aim is to complement the current descriptive approach of immune cell evaluation in biopsies with reproducible measures of density and spatial distribution of lymphocytic infiltrates below the thresholds for rejection defined by the Banff-classification. We integrate the “snapshot” of a biopsy with insights into the dynamics of lymphocyte clustering from an agent- based mathematical model that simulates tertiary lymphoid organ (TLO) formation. Material and Methods: Digital whole slide images of CD3/CD20 duplex staining in a series of 118 protocol and indication biopsies of long-term functioning renal allografts from 36 patients were investigated using a workflow automatically detecting regions of interest (ROIs), establishing density maps for lymphocytes based on a novel classification and data exchange concept (”results container”), and applying a graph-based tool to identify cell compartments and describe their spatial organization in comparison to in-silico predictions on patterns of early TLO formation. Results and Conclusion: We provide a repository of lymphocytic infiltrates observed in absence of severe rejection and provide a scalable framework for human renal biopsy analysis that is currently being adjusted to the requirements of individual translational medicine projects. The results are being used as a reference data base to identify prognostic infiltrates below the Banff threshold. The advanced digital pathology workflow comprehensively characterizes the composition of lymphocyte clusters, measures local segregation into areas enriched for T- or B-cells, detects candidate regions for early stages of TLO formation, and allows comparisons of observed patterns with predictions from a mathematical model of TLO formation.

In-silico insights on the prognostic potential of immune cell infiltration patterns in the breast lobular epithelium

SYSIMIT

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Motivation: Lymphocytic lobulitis (LLO) is a lymphocyte-predominant inflammation of lobular structures in the mammary gland tissue of patients with increased familial breast cancer risk and clinically manifest cancer. Our aim is to understand role of LLO in oncogenesis, to distinguish it from physiological immunological responses, and to determine its prognostic value in the inflammatory microenvironment associated with breast cancer. Methods and Material: We develop a multiscale cell-based model for the interactions between immune and epithelial cells in lobular epithelium with normal cell turnover rates during the menstrual cycle and simulate perturbations of the system by increased rates of epithelial damage due to impaired DNA repair, e.g. by BRCA1/2 mutations. Model-based predictions are compared to observations in tissue from women who underwent prophylactic mastectomy due to an increased risk of hereditary breast cancer, and with LLO in clinically manifest breast cancer. Physiological parameters are calibrated based on comprehensive spatial data extracted from digital whole-slide images (WSI) from a cohort of 22 healthy women who underwent reduction mammoplasty (RM). Results: We show that recurrent infiltration by immune cells occurs during physiological menstrual cycles and normal hormone levels and systematically analyze parameter perturbations that may potentially lead to malignant events. In particular, we define lobular inflammation patterns associated with increased epithelial cell turnover rates due to different hormone levels, length of the menstrual cycle, and impaired DNA-repair mechanisms due to BRCA1/2 mutations. Conclusions: Our findings indicate that the immunological context, defined by the immune cell density, functional orientation and spatial distribution, contains prognostic information previously not captured by conventional diagnostic approaches. The model analysis provided a better understanding of the role of inflammation in breast lobular epithelium, and facilitates companion biomarker discovery guiding immunomodulatory therapeutic interventions.

Identification and Characterization of Novel Small Molecule Nrf2 Modulators

SMOOSE

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The transcription factor Nrf2 is a critical regulator of cellular responses to oxidative and electrophilic stresses as well as inflammation. Therefore, Nrf2-deficiency was shown to be associated with aggravated inflammatory phenotypes in numerous murine models including sepsis and pleurisy. Consequently, Nrf2 activation attenuates inflammation and additionally fosters cancer chemoprevention. On the contrary, aberrant Nrf2 activation has been linked to increased resistance to radio- and chemotherapy. In the absence of oxidants and electrophiles, Nrf2 is constantly ubiquitinylated and degraded through binding to Keap1, an adaptor protein of E3 ubiquitin ligase. Xenobiotic stress, however, prevents Nrf2 from degradation and results in accumulation of Nrf2 and its subsequent nuclear translocation. Upon heterodimerization with small Maf proteins, the transcription of antioxidative stress-response genes is initiated. Furthermore, anti-inflammatory effects connected to Nrf2 activation arise in a reactive oxygen species-independent manner but instead via direct inhibition of pro-inflammatory cytokine gene transcription. Due to its critical role in anti-inflammatory as well as anti-oxidative pathways, Nrf2 has evolved to an attractive drug target in both academia and industry. To further investigate and elucidate the complex functions of the transcription factor Nrf2 in these regulatory systems, we aim at the development of novel Nrf2 modulators serving as innovative chemical probes for in vitro and in vivo diagnostic and therapeutic purposes.

Role of Atg16l1 in regulating temporal changes in intestinal microbiota during pregnancy

SysINFLAME

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Background: Pregnancy represents an altered state where the anatomy and physiology along with the immunity of the body gets affected. Pregnancy can be considered a unique physiological state which is temporarily created to prevent any damage to the fetus and is thus very important for the conservation of species. Along with the host physiology, the host associated microbiota (vaginal and intestinal) also gets perturbed during pregnancy. However, these alterations in the light of host genetic makeup remain largely unknown.
Aim: To elucidate host physiology and microbiota interaction longitudinally at various phases of pregnancy in genotype dependent manner.
Methods: We employed mice conditionally lacking Atg16l1 gene in intestinal epithelial cells (Atg16l1ΔIEC), where Atg16l1fl/fl mice served as control group. In order to understand the effect of gestation on gut microbiota in genotype dependent manner, the fecal samples were collected before (baseline), during (trimester 1, 2 and 3) and after pregnancy from both genotypes (Atg16l1fl/fl and Atg16l1ΔIEC; n=7/genotype). Fecal microbiota was investigated taxonomically and functionally using 16S rRNA gene (V3-V4 variable region) and shotgun metagenome sequencing. Furthermore, to study the host response, one set (n=4) of pregnant and nulliparous non-pregnant (n=5) mice at day 0 and trimester 3 were also analysed.
Results: Pregnant Atg16l1ΔIEC mice showed significant increase in caecum weight along with increased levels of cytokines namely Cxcl1, Il10 and TNFα as compared to the Atg16l1fl/fl. A general increase of Lactobacillus was noted at trimester 3 of pregnancy in both genotypes, however, the increase in Atg16l1ΔIEC was noticeably reduced as compared to Atg16l1fl/fl. β-diversity analysis showed that pregnancy makes shift in microbial profile from day 0 to T3 in both genotypes nevertheless these shifts were dominant and unique in Atg16l1ΔIEC mice. Metagenomic analysis showed that histidine, proline and lysine biosynthesis was significantly higher in the Atg16l1ΔIEC samples at baseline and trimester 3 as compared to the Atg16l1fl/fl.
Conclusion: Atg16l1 is likely to promote the development of conducive microbiota that is beneficial in maintaining pregnancy.

Molecular Profiling and Diagnostic Potential of Extracellular Vesicles in Inflammatory Bowel Disease (IBD) and Colorectal Cancer (CRC)

SysINFLAME

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Understanding complex physiological and pathological processes of gut inflammation and its possible progression to CRC remains a persistent challenge. There is also an ongoing unmet need for reliable biomarkers to help in management of these diseases. The relevance of exosomes or extracellular vesicles (EVs) has been recently reshaped from just being naive cellular debris, and emerged as mediators of cell-cell communication, manipulators of immunity, and promoters of disease progression. EVs can, for instance, induce/propagate inflammation signals and drive pre-metastatic niche formation. EVs can be readily isolated from body fluids, protect their cargo, and reflects the cells of origin and disease activity. In addition to RNA and proteins, DNA has been recently discovered in EVs. Therefore, profiling EVs-associated cargo can provide important biological and mechanistic insights and regarded as a fingerprint of these diseases. To this end, using optimized isolation and molecular profiling protocols, we investigated EV-associated cargo at different levels of analysis. Firstly, we demonstrate for the first time that the enrichment of circulating miRNA carriers can allow a more reliable identification of disease-related miRNAs, which better reflect disease tissue-related patterns. Secondly, two-dimensional multiplex-fluorescence gel electrophoresis and mass spectrometry analyses revealed distinct protein patterns of IBD and CRC, independent of the EVs isolation method. Thirdly, next-generation sequencing analyses indicated drastic differences between IBD and CRC, and identified over 200 differentially expressed RNAs, as well as various variations and “somatic” mutations in genomic and mitochondrial DNA. More interestingly, based on physical and optical phenomena, there is an ongoing effort to develop biosensor chips for naked-eye detection of IBD/CRC-related EVs. Our findings thus demonstrate a high potential diagnostic value of EV-based biomarkers of IBD and CRC.

Gut microbial profiles of German primary sclerosing cholangitis patients in comparison to ulcerative colitis patients and healthy controls

SysINFLAME

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Primary sclerosing cholangitis (PSC) is a chronic inflammatory and fibrosing disease of the bile ducts with progressive condition and of unknown etiology. A co-occurrence of inflammatory bowel disease (IBD) with the clinical picture of a mild pancolitis is described in 60-80% of PSC patients. As the intestinal microbiota was reported to be altered in several metabolic and inflammatory diseases and recent reports also suggest a microbial involvement in PSC, we aimed to further investigate the PSC-specific intestinal microbiome and to distinguish it from the ulcerative colitis (UC)-specific and PSC+UC-specific microbial composition. For this purpose, we extracted the DNA from faecal samples of 98 healthy controls (HC), 35 PSC patients (PSC), 38 PSC patients with concomitant UC (PSC+UC) and 88 subjects with UC (UC) and applied it to a dual-barcoding high-throughput sequencing approach targeting the v1-v2 region of the 16S rDNA. A first analysis of alpha diversity showed no significant differences between the four groups. However, PSC+UC patients' profiles had an intermediate diversity between PSC and UC. The microbial dysbiosis index was significantly increased in PSC, UC and PSC+UC compared to HC. Beta diversity measurements showed a clear differentiation in the overall microbiome of PSC, PSC+UC and UC compared to HC, whereas a difference between PSC and PSC+UC could only be seen in the unweighted UniFrac distance (measuring absence and presence of bacterial taxa). Again, PSC+UC showed an intermediate pattern between PSC and UC. Differences in taxa abundances implicated Proteobacteria to be more abundant in the three diseased groups in comparison to HC. On genus level, Parabacteroides, Streptococcus, Burkholderia and Propionibacterium showed a higher abundance in PSC compared to HC, whereas Prevotella seemed to be decreased. Furthermore, we could confirm that Veillonella are more abundant in PSC compared to HC, but we did not find a clear difference between PSC and UC, which is in contrast to already published results. Some taxa differentiated the microbial profiles of PSC and HC in our data, but were not able to discriminate between UC and PSC.

Hypothalamic inflammation in human obesity is mediated by environmental and genetic factors and is not reversed by bariatric surgery

SysINFLAME

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Obesity is known to be associated with hypothalamic inflammation in animal models. In the present study we examined the mediobasal hypothalamus (MBH) of 57 obese human subjects and 54 ageand sex- matched non-obese controls by MRI and analyzed the T2-hyperintensity as a measure for hypothalamic inflammation. Obese subjects exhibited a T2-hyperintensity in the left but not the right MBH which was strongly associated with systemic low-grade inflammation but not with peripheral insulin resistance. MR-spectroscopy revealed the number of neurons in the left MBH being similar in obese versus control subjects suggesting functional but not structural impairment due to the inflammation process. To gain insights into the mechanisms driving hypothalamic inflammation we performed nutritional analysis and 16S rRNA gene gut microbiome sequencing showing that a high-fat diet induces a reduction of the Parasutterella sp. in the gut being significantly correlated to MBH-T2-hyperintensity. In addition to these environmental factors, we found that subjects carrying common polymorphisms in the JNK but not the FTO gene were more susceptible to hypothalamic inflammation. In a subgroup analysis, a human intervention by bariatric surgery had no effect on MBH-T2-hyperintensity despite a significant weight loss and improvement of peripheral insulin sensitivity. In conclusion, obesity in humans is associated with hypothalamic inflammation being caused by disturbances in the gut-brain axis due to environmental and genetic factors. The finding that a profound weight loss due to bariatric surgery does not beneficially influence MBH-T2-hyperintensity might suggest that additional measures should be developed targeting hypothalamic inflammation by nutritional and/or pharmacological interventions.

NOD2 affects microbial resilience after antibiotic treatment in mice

SysINFLAME

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Microbial communities are important for physiological homeostasis in the mammalian gut. Understanding how the microbiota interacts with the host's genotype, to respond to antibiotics as a selective pressure, is crucial to determine how stability of community composition is maintained. Concerns related to the use of antibiotics include pathogen resistance, alterations of the microbial composition, and acute and chronic health problems. The increasing rates of autoimmune diseases and chronic intestinal disorders, e.g. inflammatory or chronic infections, have been hypothesized to be related to a disturbed resilience. Using a mouse model deficient in the Crohn's Disease risk gene, NOD2, we investigated the role of this innate immune receptor for microbial resilience after a perturbation. Wild-type C57BL6(WT) and knock-out NOD2(KO) mice were treated for two weeks with a broad-spectrum antibiotic cocktail and the fecal microbial composition was followed for 10 weeks. Using 16S rDNA phylogenomic analysis (V3-V4 region), we determined community composition. Additionally, we assessed the occurrence of selected known resistance genes using qPCR. Our results confirmed the presence of antibiotic resistance genes, where a significant difference was observed post-antibiotics (p-value=0,048). Of note, most resistance genes were associated with the phylum Proteobacteria, of which Escherichia/Shigella were the dominant genera in both genotypes during the 2 weeks of antibiotics. Additionally, relative quantification confirmed the expansion of Proteobacteria during this period. Furthermore, antibiotic administration altered the composition of the microbial gut community in both genotypes. Interestingly, in NOD2 KO mice, this lead to long-term changes in the community composition, which did not resolve, even after 10 weeks. Thus, our results demonstrated a phenotypic variation, where the NOD2 genotype impairs resilience of the gut microbiota leading to a delayed recovery.

Association of atopic dermatitis with cardiometabolic diseases and risk factors

SysINFLAME

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Atopic dermatitis (AD) has been recently reported to increase the risk for cardiovascular diseases in adults, as well as related risk factors in children. These findings were mainly reported for US populations. Therefore, in the present analysis, we aim to investigate the association of AD with cardiometabolic diseases and related risk factors using data of three German cohorts of children and adults: a prospective analysis using data of 1925696 subjects of the cohort of German National Health Insurance beneficiaries, a cross-sectional analysis of 2990 individuals of the KORA F4 cohort and a longitudinal analysis of 3665 participants of the 10 and 15 year follow-ups of the GINIplus and LISAplus birth cohort studies. None of the adjusted regression models yielded significant associations of AD with any of the tested cardiometabolic diseases or related risk factors. In a sensitivity analysis of the German National Health Insurance beneficiaries, after further adjustment for health care utilization behavior (i.e. the total number of physician contacts due to reasons other than AD), AD was associated with decreased risk of stroke, type 2 diabetes, hypertension, and higher risk of angina pectoris in the sub-group of AD patients with systemic medication. These findings were limited to patients more than 40 years old and, except for stroke, stronger in patients with more severe AD. When analysing the GINIplus and LISAplus cross-sectionally, a direct association between HDL and AD was observed at age 15 years. Our findings do not confirm the hypothesis that AD is a risk factor for cardiometabolic diseases and risk factors. To the contrary, sensitivity analyses indicate an inverse association, if any.

Dynamic changes of the immune repertoire of IBD patients during different biologic therapies

SysINFLAME

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Inflammatory bowel disease (IBD) is characterized by chronically remittent intestinal inflammation, influenced by environmental, microbial and immunological cues in genetically susceptible individuals. T cells are primary mediators of chronic inflammation and contribute to the pathogenesis of inflammatory diseases. Despite the importance of T cells in inflammation, comprehensive data about dynamics of the T cell populations and their T cell receptor (TCR) repertoire in IBD are scarce. While the standard treatment of IBD involves the administration of corticosteroids and other immunosuppressive drugs, these often lose their efficacy while the disease progresses. Anti-TNF antibodies (e.g. Infliximab) have become the favored option for severe cases of IBD, which do not respond to standard treatment. However, the systemic effect on the immune system may induce adverse outcomes in patients with certain co- morbidities. Recently, Vedolizumab, an antibody against the α4β7 integrin expressed by T cells homing to the intestinal mucosa, was approved by the US Food and Drug Administration as an alternative more gut-specific treatment for IBD. Here, we present a comprehensive study of T cell populations in patients with ulcerative colitis (UC) and Crohn's disease (CD) before and after 14 weeks of treatment with either Infliximab or Vedolizumab. To this end, we have performed immunophenotyping of cells isolated from peripheral blood, as well as intestinal compartments, alongside TCR profiling of intestinal T cells. Despite strong inter-individual differences, treatment with Vedolizumab appears to reduce the frequency of activated CD4 + T cells in the intestine. TCR profiling revealed biased usage of VJ region combinations in different patient groups. Together, these methods, combined with correlative analysis of the patients' clinical response, will provide insight into the mechanisms underlying treatment efficacy and failure and will help identify disease-relevant T cell subsets.

Integrated Research Data Management System of sysINFLAME

SysINFLAME

Presenting Author: Ulrich Sax

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Introduction. Multi-omics driven research, for example for complex inflammatory diseases as in sysINFLAME requires a thorough data management plan from the measurement of the data to the integration and subsequently systems medicine analyses. Methods. Firstly, the relevant research aspects have to be gathered in an appropriate data model considering patient consent information, data quality measures and data privacy. Secondly, research in a consortium implies a multi-centric data generation and often communication across different local area networks. Results. We here present a central access point for an exemplary multi-center research group as a solution for checking in heterogeneous data snippets, offering structured data sets, the possibility of annotating the data with additional meta data and a central overview of the available data sets. Elaborate governance processes allow transparent data use and access described in a consolidated use and access policy (UAP). In parallel, researchers can explore the integrated data sets using the integrated data model for filtering and selecting distinct data sets according to the UAP. Pre-defined analyses can be performed on this data on the fly, more elaborate analyses can be plugged in using a simple R-plugin mechanism. Discussion. We here present as a role model our integrated Data Management System developed for our e:Med sysINFLAME consortium. As expected, consenting data models and access policies are of equal complexity like the technical infrastructure. Keywords. Medical Informatics Application, Data Curation, Information Storage and Retrieval, Computer Security, Data Collection, Use and Access, Policies

The role of the Ikba gene family member NFKBIZ in colitis associated cancer

Presenting Author: Go Ito

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Inflammatory bowel disease (IBD) is a relapsing-remitting chronic inflammatory disorder. Importantly, the risk of developing colorectal cancer is increased in IBD patients with chronically active disease. Colitis-associated cancer (CAC) has different characteristics compared to sporadic colorectal cancer, such as highly invasiveness at an early stage and onset of carcinogenesis in younger patients. To investigate the genetic basis for these differences, we used the AOM/DSS murine model of CAC. Using whole exome as well as the whole transcriptome sequencing of tumor and colonic non-tumor samples, we determined the mutational landscape to identify recurrent mutations, which may be of functional relevance for the malignant transformation. Using this approach, we identified several tumor-associated variants in the NFKBIZ gene. NFKBIZ is a member of the Iκbαgene family and is known to be induced by IL1β in hematopoietic cells. However, the precise role of NFKBIZ in human intestinal epithelial cells (IECs) remains largely unknown. In our study, we first analyzed the regulation of NFKBIZ expression in intestinal cell lines. To perform functional studies, we created cell lines that are deficient for NFKBIZ by using the CRISPR/Cas9 system. We found that NFKBIZ-deficient cells showed impaired autophagy and enhanced ER stress, which are associated with chronic inflammation. We could also show that NFKBIZ deficient cells exhibited impaired proliferation. Interestingly, expression of NFKBIZ is upregulated in IECs of UC patients suggesting that overexpression of NFKBIZ could induce a hyperproliferative state potentially promoting tumorigenesis. In addition to cancer cell lines we also use human organoids as a model. Here, NFKBIZ is also induced by IL1β stimulation and expression of NFKBIZ is stably upregulated in organoids derived from UC patients. Taken together these results point to a potential role of NFKBIZ in the pathogenesis of CAC and warrants further investigation.

Genome-Wide Integrative Analysis of T Helper Cells

Presenting Author: Linda Krause

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T helper cells play a key role in the adaptive immune system. In the last decade, subsets of known T helper cell grew from two (Th1 and Th2) to over five (Th1, Th2, Th9, Th17, Th22 and Treg cells). The state of the art of identification is according to secreted cytokines, protein expression of transcription factors and presented surface molecules. However, there is substantial plasticity in-between the different subsets, reflected e.g. by Th1 cells that also secret interleukin 17, the signature cytokine of Th17. The aim of our study is to deeply analyse distinct T cell subsets allowing a comprehensive phenotypic description and explaining the mechanisms of plasticity. To achieve this aim, we generated 60 human T cell clones derived from biopsies or blood of chronic inflammatory skin diseases and investigated their phenotype on protein, mRNA and epigenetic level by using Bioplex assays, whole transcriptome expression and methylation arrays, respectively, in a matched analysis setting. Comparing several clustering methods applied on the secreted cytokines seven groups of T helper cells were identified, whereof three represent novel subsets. First, we thoroughly characterized these groups on the transcriptional level and identified phenotype specific markers. Next, we analysed the markers for stability by combining transcriptional information with methylation data using complex statistical regression models. With this genome-wide integrative approach, we intend to improve the understanding on T cell diversity allowing a precise therapeutic modulation and targeting of T cells.

e:Med
SYSTEMS MEDICINE

Poster Presentations

Cross-topic Issues II – Heterogeneity of Disease

MyPathSem: From Data to Pathways

i:DSem –myPathSem

Presenting Author: Ulrich Sax, Frank Kramer

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Introduction. Translational research offers rich high dimensional data sets to physicians in several disease domains. These datasets are usually not integrated with other patient data or annotated with current literature and open data. Therefore they are not instantly useful in the individual clinical context. This puts a high burden on researchers and physicians who have to collect, integrate, interpret and present this data the closer it gets to individual case decision support like in tumor boards. Methods. We analyze current and anticipated future high throughput data sources in order to combine them with low dimensional patient data and provide a front end for querying, filtering and visualizing the data. Furthermore, we enrich this data with current literature knowledge as well as open data sources and develop a method to generate highly condensed, context-specific signal networks on the basis of the presented individual integrated data set. Preliminary Results. We extracted and integrated several low dimension data types from clinical context (e.g. quality controlled clinical cancer registry data and data from an electronic patient record. This data is integrated and presented in tranSMART. Furthermore, we integrate knowledge about signaling pathways from pathway databases in R using the rBiopaxParser and display these pathways on an Angular- and Cytoscape.js-based frontend. Discussion and Outlook. We evaluate the usefulness of our environment in two concrete research environments. Towards the end of the project, our integration and analysis tools will be published and made available within the genXplain platform. Keywords. Medical Informatics Application, Information Storage and Retrieval, Data Collection, Use and Access, Network Analysis, Pathway Knowledge

Reference point insensitive molecular data analysis

MMML-Demonstrators

Presenting Author: Michael Altenbuchinger

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In biomedicine, every molecular measurement is relative to a reference point, like a fixed aliquot of RNA extracted from a tissue, a defined number of blood cells, or a defined volume of biofluid. Reference points are often chosen for practical reasons. For example, we might want to assess the metabolome of a diseased organ but can only measure metabolites in blood or urine. In this case the observable data only indirectly reflects the disease state. The statistical implications of these discrepancies in reference points have not yet been discussed. Reference points are closely linked to data normalization and preprocessing. If we normalize data to a common mean, we generate a data internal reference point: each measurement of a specific feature is expressed relative to the mean of all features. For instance, gene expression profiling measures abundances of mRNA transcripts and normalization to a common mean gives abundances relative to the mean expression level of all genes. This prescription is not unique, e.g. profiles can be normalized to a constant value of one or several housekeeping features. In the latter case we choose another data internal reference point: the mean of the housekeeping features. Here we show that reference point discrepancies compromise the performance of regression models like the LASSO. As an alternative, we suggest zero-sum regression for a reference point insensitive analysis. As the LASSO, zero-sum regression performs feature selection by penalizing the l1 norm. However, zero-sum regression additionally enforces the sum over the regression weights to equal zero. This constraint has important practical implications. First, we are unbiased concerning the “best” reference point (or “best” normalization). Second, sparse zero-sum models are “truly sparse”. We illustrate these two aspects by contrasting zero-sum regression with the standard LASSO in a simulation study and in an application that integrates intestinal microbiome analysis with metabolomics. Furthermore, we illustrate that zero-sum regression yields universal models that apply beyond specific platforms. This is demonstrated for the classification of diffuse large B-cell lymphomas into their cell-of-origin subtypes.

A Similarity Measure for Clinical Attributes using the Kaplan-Meier Estimator

CLIOMMICS

Presenting Author: Christian Karmen

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Introduction: Systems medicine requires the analysis of data that is collected from interdisciplinary medical fields and tries to comprise them into disease models that are suitable for medical applications. Instance-based learning is a method for the modelling of decision support systems (DSS) and for case-based reasoning (CBR) based systems, which are able to incorporate any structured data independently of its origin and thus is a suitable method for systems medicine. Especially CBR is gaining a rising attention and importance since the last few years [1]. In CBR similar cases of a given case are being searched within a repository of solved cases with the help of similarity measures. This procedure supports the person of interest in his decision by considering already known solved cases that are comparable to his own. As a first step in this process the local similarities between all values of any given attribute are defined. In a second step a global similarity measure is calculated comprising all local similarities of two given cases. Expert knowledge and study results are often used in order to determine local similarities. However, the individual assessment of each attribute's value is highly subjective because of its estimations by the involved research group and thus may lead to a bias. As an alternative, similarity measures based on statistical calculations can be used, e.g. with the frequency of occurrences within the case repository [2]. Although this approach enables a prediction accuracy of 80 to 85 per cent, it may still be considered as too low for many real-world clinical applications as targeted by systems medicine. Thus, our goal is to define a high precision similarity measure suitable for clinical attributes. Material and Methods: The approach of our similarity function is to determine the relevance of each attribute by putting it in relation to its survival-based data (by using the Kaplan-Meier estimator) and by doing so to create a novel similarity measure. So as a first step we apply the Kaplan-Meier estimator with the target variable "progression-free survival" (PFS) for any value of any nominal attribute. For all non-nominal attributes (linear and continuous attributes) a discretization will be performed in advance. The calculated local similarity between two values of a given attribute depends on the area between the computed Kaplan-Meier diagrams (KMD) of those two values. Subsequently, this area will be put in relation with a reference area in order to normalize its value to the range between 0 and 1. By defining weights of attributes the impact of each individual attribute to the global similarity can be described. In order to determine the weight of a given attribute we calculate the area of its values with the worst and best overall survival in the KMD and then, like in the local similarity measure, normalize its value. As a global similarity measure of two given cases we use a form of the Euclidean metric which also considers weights for attributes.

For the implementation of our new similarity measure we used the Java framework "myCBR" [3] which was developed by the German Research Center for Artificial Intelligence (DFKI) in cooperation with the University of West London (UWL). Furthermore, we developed a graphical user interface for a stand-alone CBR application ("myCBR Builder") which enables a retrieval of similar cases based on an available similarity measure. Results: We are currently using the introduced implementation for the CLIOMMICS [4] project as part of a novel modular CBR software system which is dynamically handling a number of attributes. This system will be able to automatically process any available attributes e.g. from a harmonized data warehouse and use them for similarity estimation. Discussion: We described a novel similarity measure that is based on survival data, which therefore are mandatory in the first place. However, we expect the availability of survival data for malign and complex diseases like those that are in focus of systems medicine. It should be noted that a comprehensive validation of similarity measures in the medical field is hardly possible because the most efficient therapy for an individual patient can only, if at all, be observed afterwards. Furthermore, many therapies for malign diseases cannot be repeated to observe what the best possible outcome is. So instead of taking only the best match into account, we consider another validation approach for our future research activities where we perform a sub-cohort analysis of the most similar patients.

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References:

[1] M.M. Richter, R.O. Weber, Case-based reasoning: A textbook, Springer. Heidelberg, 2013
[2] D.R. Wilson, T.R. Martinez, Improved heterogeneous distance functions. Journal of artificial intelligence research (1997), 1–34
[3] K. Bach, K.-D. Althoff, Developing Case-Based Reasoning Applications Using myCBR 3. In: Agudo BD, Watson I, editors. Case-Based Reasoning Research and Development: 20th International Conference, ICCBR 2012, Lyon, France, September 3-6, 2012. Proceedings. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012. p. 17–31
[4] e:Med Systems Medicine, CLIOMMICS [last accessed: 2016 Jul 28]. Available from: URL:http://www.sys-med.de/en/consortia/cliommics/

Robust In-Silico identification of sequenced Cancer Cell Lines

MAPTor-NET

Presenting Author: Raik Otto

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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.

SUPR-G: Systems biology of the Unfolded Protein Response in Glioma

SUPR-G

Presenting Author: Grischa Toedt

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Tumor cells commonly exhibit high levels of endoplasmic reticulum stress which triggers the unfolded protein response (UPR), a mechanism, which recently has gained a lot of attention in the treatment of malignancies. Despite its broad clinical importance, quantitative models that systematically describe the UPR in cancer cells are missing so far. In order to lever the UPR for therapeutic intervention in glioma, strong needs exist for an integrated vision of how this molecular pathway contributes to tumor growth and infiltration. The aim of the e:Med junior research alliance SUPR-G is to combine translatome and proteome analyses, computational modeling and in vivo animal model target validation to gain novel and system-wide insights into the UPR. We have rigorously curated transcriptomic, proteomic and in vivo animal data. Each of these datasets describes different aspects of the UPR. The integrated view of these datasets will result in a comprehensive description of known and candidate UPR protein networks and modules, which can serve as a resource for understanding UPR related pathogenic mechanisms.

Modelling telomere maintenance mechanisms in tumour cells

CancerTelSys

Presenting Author: Alexandra Poos

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Telomeres are nucleoprotein structures at the ends of the eukaryotic chromosomes protecting them against fusion, degradation and unwanted double-strand break repair mechanisms. The length and structure of telomeres is tightly controlled. Telomeric DNA is composed of repetitive sequences and can be de novo synthesized by the reverse transcriptase telomerase, which normally is only active in stem cells and not expressed in most somatic cells. Due to the end-replication problem and nucleolytic processing telomeres in somatic cells thus shorten gradually with each cell division. The accumulation of critically short telomeres leads to replicative senescence or apoptosis, thereby preventing unlimited proliferation. Cancer cells overcome this restriction by maintaining their telomeres by either re-expressing telomerase or employing mechanisms based on homologous recombination, called alternative lengthening of telomeres (ALT). Understanding the mechanisms that maintain telomere length has substantial medical implications, in particular for ageing and carcinogenesis. To study the regulation of the telomerase reverse transcriptase (TERT) gene in cancer we used our Mixed Integer Linear Programming approach that we have developed recently. The aim was to identify the most important transcriptional regulators of TERT between different cancer types as well as the most common ones among several cancer entities. To this end we used RNA-Seq data from The Cancer Genome Atlas (TCGA) as well as regulator binding information from different databases (e.g. MetaCore, Chea, Encode, etc.). We identified PITX1 as a prostate cancer specific TERT regulator. PITX1 is involved in the HIF-1A response and has a repressive effect on TERT expression. Furthermore, we are establishing a classification system to distinguish between the different telomere maintenance mechanisms (TMM). For this we combine specific cytogenetic TMM features (e.g. presence of utrabright telomere foci, extrachromosomal telomeric repeats, ALT-associated PML bodies), genetic variants (e.g. TERT promoter mutations, mutations in the gene ATRX, etc.) and RNA-Seq data of pediatric glioblastoma as well as neuroblastoma. The computional approaches presented here contribute to a better understanding of how cancer cells maintain their telomeres and thereby their ability of unlimited proliferation.

An approach towards predicting melanoma cell death induced by 2nd generation TRAIL receptor agonist IZI1551 in single and combination treatment with IAP antagonist TL32711/Birinapant

Melanoma sensitivity

Presenting Author: Markus Rehm

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2nd generation TRAIL receptor agonists, such as IZI1551, hold great potential to induce cell death in otherwise highly resistant cancer cells, such as melanoma. Combination treatments with targeted therapeutics from the class of IAP antagonists may further enhance treatment efficacy. However, due to the high heterogeneity found within melanoma and other difficult-to-treat cancers, responsiveness cannot be predicted confidently on a case-by-case basis. Furthermore, unsuccessful treatments with costly novel drugs are now becoming an unbearable burden for health care sectors internationally. Consequently, tools that can predict individual treatment responsiveness are required. In this project, we aim (i) to capture the response heterogeneity of melanoma cell line models to IZI1551 treatments, alone or in combination with IAP antagonist Birinapant, (ii) to study whether responsiveness can be predicted from expression patterns of key regulatory proteins analysed within the context of TRAIL signalling topology and pattern recognition approaches, and (iii) to expand predictive capacity from 2D to 3D melanoma growth conditions as a prerequisite for subsequent translational studies. By now, we have measured the response heterogeneity of 12 melanoma cell lines from progressing disease stages and from diverse mutational backgrounds for 25 treatments conditions. As expected, we observed substantial response heterogeneity, with resistance, single-treatment responsiveness as well as synergism or potentiation being detected. We now determine pre-treatment expression amounts of key TRAIL pathway components in 2D and 3D growth conditions and will apply an established data processing and systems modelling pipeline to evaluate whether treatment responsiveness can be confidently predicted.

The Hippo-YAP1-pathway is activated in relapsed and MYCN amplified neuroblastoma

SMOOSE, SYSMED-NB

Presenting Author: Kerstin Schönbeck

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Neuroblastoma is the most common extracranial solid tumor of childhood, originating from neural crest progenitors of the sympathetic nervous system. Relapse occurs in more than 50% of patients with high risk neuroblastoma, and relapsed neuroblastoma is almost always fatal. Amplification of the MYCN, present in 50% of high risk neuroblastoma, is an adverse prognostic factor and correlates with metastatic disease. Identification of druggable targets in high-risk and relapse neuroblastoma is a prerequisite for the development of novel treatment strategies. Analyzing primary and relapsed neuroblastomas from 23 patients using whole exome sequencing and RNA expression profiling, we found relapse-specific activation of the Hippo-YAP1-pathway. The Hippo-YAP1-pathway regulates organ size and is known to be activated in various tumor entities such as lung, liver or ovarian cancer. Analysis of YAP1 protein- and mRNA-expression in neuroblastoma cell lines revealed high expression levels in a fraction of neuroblastoma cell lines correlating with the presence of MYCN amplification. We now are further investigating the effect of YAP1 overexpression or downregulation on the proliferation, apoptosis, migration and differentiation of neuroblastoma cells.

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

SysINFLAME

Presenting Author: Hansjörg Baurecht

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

Targeted gene panel sequencing for early-onset inflammatory bowel disease

SysINFLAME

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In contrast to adult-onset inflammatory bowel disease (IBD), where many genetic loci have been shown to be involved in complex disease etiology, early-onset IBD (eoIBD), with a disease onset during the first ten years of life, can sometimes present as a monogenic condition. As a result, the clinical phenotype and ideal disease management in these patients often differ from those in adult-onset IBD. However, due to high costs and the complexity of data analysis, routine screening for genetic causes has not yet become a standard part of the diagnostic process in eoIBD patients. Genes associated with monogenic IBD were selected and targeted panel sequencing involving 28 or 56 genes was performed for 89 patients diagnosed with eoIBD. The results were compared to whole-exome sequencing (WES) data available for 30 of the patients and screened for causative variants. Average coverage of target region bases was more than ten-fold higher in the targeted gene panel sequencing (492x) compared to WES (42x) and both methods were able to detect all 496 on-target variants. Six patients were given a distinct genetic diagnosis based on variants affecting genes of the IL10 signaling pathway (interleukin 10 receptors A and B; three patients), WAS (Wiskott-Aldrich syndrome), MYO5B (myosin Vb) and DKC1 (dyskeratosis congenita 1, dyskerin). Variants in TTC7A (tetratricopeptide repeat domain-7A; two variants in one patient) and RTEL1 (regulator of telomere elongation helicase 1) were classified as affecting the protein function, however not in terms of truly Mendelian traits. Additional variants in RTEL1, TTC7A and WAS classified as likely affecting the protein function are currently undergoing functional testing in three additional patients. Based on these findings, we conclude that targeted gene panel sequencing is a fast and effective screening method for monogenic causes of eoIBD that needs to be routinely established in national referral centers.

Small, dense LDL cholesterol is a cardiovascular risk factor in several chronic inflammatory diseases

SysINFLAME

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Introduction: Subjects with Chronic inflammatory diseases (CID) exhibit a profound increase of cardiovascular risk (CVR) resulting in reduced life expectancy. At the same time LDL-cholesterol serum levels seem to be low in these patients suggesting a special type of “rheumatic dyslipidemia”.

Patients and Methods: In our mono-centre, longitudinal, observational study small dense LDL-cholesterol (sdLDL) was measured in n=141 subjects with CID (Rheumatoid Arthritis n= 59, Inflammatory Bowel Disease n= 35, Ankylosing Spondylitis n= 25, Psoriasis n= 22) at baseline, 6 and 26 weeks after initiation of different anti-cytokine therapies (anti-TNFα, anti-IL-6). Age-, BMI- and sex-matched subjects (n=141) served as healthy controls.

Results: CID patients exhibit a significant increase in the sdLDL/LDL ratio at baseline independent of the kind of CID compared to controls. Interestingly, while anti-cytokine treatment induced a profound improvement of the CID (as measured by disease activity scores and CRP-levels), none of the biological agents affected the sdLDL/LDL ratio in a time period of 6 and 26 weeks.

Conclusion: While anti-cytokine therapies exhibit a dramatic improvement of the CID, the “rheumatic dyslipidemia” is not affected by such agents. This suggest that Endocrinologists and Diabetologists should be involved in the standard patient care in CID in order to improve CVR- factors by additional diagnostics and therapies to extent patients life-expectancy to normal.

Long non-coding RNA RP1-79C4.4 as novel candidate gene for atrial fibrillation?

symAtrial

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Background: Atrial fibrillation (AF) is the most common arrhythmia in the general population. It was demonstrated by multiple epidemiological studies that AF has a heritable component. In this regard, genome-wide association studies already revealed numerous single-nucleotide polymorphisms (SNPs) in 14 distinct loci (KCNN3, HCN4, ZFHX3, PITX2, SYNE2, SYNPO2L, CAV1/2, NEURL, TBX5, CUX2, CAND2, GJA1, C9orf3 and PRRX1). However, the molecular mechanisms underlying these loci and the extent to which those variants contribute to AF is unclear. The aim of this project is to identify novel candidate genes for AF and their molecular characterization.
Methods: Expression quantitative trait loci (eQTL) analysis with all published AF-related SNPs was performed in the genotype-tissue expression (GTEx) project in order to identify AF candidate genes. Significant novel eQTLs (P < 1e-5) were considered for further expression analysis in atrial tissue from the AF_CCS cohort (n > 450) using a designed duplex taqman assay. AF_CCS is a clinic-based cohort of various well-phenotyped AF patients (lone AF, acute AF, high-risk AF, postoperative AF) with an established biobank. Biomaterials for the analysis include cardiac tissue and blood samples (n=118).
Results: The bioinformatical analysis revealed among six cis-eQTL genes the long non-coding RNA (lncRNA) RP1-79C4.4 as novel functional candidate. This so far uninvestigated lncRNA RP1-79C4.4 was upregulated with the homozygous C allele of rs629234 in tissue of the left ventricle. This lncRNA is located in the first intron of the PRRX1 gene and consists of 2045 bp. Intriguingly, the PRRX1-encoded protein, a member of the homeobox transcription factors, has already been shown to be associated with AF. Preliminary expression analysis of the lncRNA showed the detection of unspliced pre-mRNA of PRRX1 in addition to the lncRNA RP1-79C4.4. A duplex taqman assay was successfully established to measure the lncRNA as well as the PRRX1 pre-mRNA.
Conclusion: We identified the lncRNA RP1-79C4.4 within the PRRX1 gene to be associated with the AF-related SNP rs629234. So far, the role of the lncRNA RP1-79C4.4 during AF is completely unknown as well as its general function and regulation. It poses an interesting new candidate for AF and will be now further characterized.

LPPdb: a database for integration of structural, functional, biological and clinical information on oxidized lipids based biomarkers

SysMedOs

Presenting Author: 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 disease pathogenesis the information on their structures, activities and functions as well as associations with various pathological conditions need to be collected and summarized via integrated knowledge database. The importance of such databases was illustrated on large-scale genomics and proteomics projects, where established databases and gene ontology are applied for analyzing high-throughput experiments, evaluating the biological significance, and formulating functional hypotheses. Here we present LPPdb, a first database aiming to accumulate current knowledge on oxidized lipids, structure the information, and provide the community with a resource useful for researchers from chemistry, biology, medicine, and clinics. Each LPPdb entry is annotated based on its chemical identity, parent compound, structural information, identification and quantification protocols, type of the biological material it was identified (cell culture, animal models, clinical materials), published evidences of involvement in pathology and known biological pathways. LPPdb will provide a platform to scientists from academia, clinics and industry to support the identification of different LPP species form high-throughput lipidomics for biomarker discovery and validation and thus help to determine "biomarker signatures" to assess pathological processes.

Poster Presentations

Specific Diseases II - Neuropsychiatric Disorders

Dynamic reconfiguration of brain networks: links to schizophrenia risk and NMDA receptor function

IntegraMent

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Introduction:
Schizophrenia is increasingly recognized as a disorder of distributed neural dynamics, but the molecular and genetic contributions to the network abnormalities are poorly understood(Meyer-Lindenberg 2010). Recent theoretical and experimental work has linked these large-scale phenotypes to disturbances in the N-Methyl-D-Aspartate (NMDA) dependent cellular excitation-inhibitory balance resulting in impaired neural synchrony on the system level(Uhlhaas 2013). Here, combining novel techniques from dynamic network neuroscience, intermediate phenotype (IP) studies, and pharmaco-fMRI we investigate the dynamics of temporal disintegration or “network flexibility”, a measure of the dynamic reconfiguration of the community structure of time-variant brain networks constructed from fMRI time series (Braun, Schafer et al. 2015).

Methods:
We examined 37 unaffected first-grade relatives, 28 schizophrenia patients and 139 healthy controls with functional magnetic resonance imaging (fMRI) during a well-established working memory paradigm. We identified alterations in the dynamic reconfiguration of functional brain networks using a multilayer-community detection algorithm and quantified the changes in the time-variant brain community structure using a measure of temporal disintegration or “network flexibility” (a measure of how often brain nodes changes their community allegiance)(Bassett, Wymbs et al. 2011). To further assess a plausible intermediate signaling pathway in relation to the proposed alterations in the cellular excitation-inhibitory balance, we conducted a second observer-blind, placebo-controlled, cross-over pharmacological challenge study in an independent sample of 37 healthy controls receiving a dose of the NMDA receptor antagonist dextromethorphan (DXM).

Results:
Controls, first-grade relatives and patients showed significant differences in network flexibility ($F(2,196) = 6.541$, $p = 0.002$) in an ordinal pattern consistent with the assumed genetic risk load of the groups (highest for patients, intermediate for relatives, lowest for controls). NMDA receptor antagonism significantly enhanced network flexibility in healthy subjects DXM, (repeated measures ANOVA: $F(1,34) = 5.291$, $p = 0.028$)).

Conclusions:
Our results provide evidence for a potential dynamic network intermediate phenotype related to the genetic liability for schizophrenia manifesting as disintegrated configuration of brain networks during executive function. The phenotype is influenced by NMDA receptor antagonism in a direction that is consistent with the alterations in relatives and patients and the role of glutamate function as molecular intermediate in the temporal coordination of neural networks and the pathophysiology of schizophrenia.

References:
Bassett, D. S., N. F. Wymbs, M. A. Porter, P. J. Mucha, J. M. Carlson and S. T. Grafton (2011). "Dynamic reconfiguration of human brain networks during learning." Proc Natl Acad Sci U S A 108(18): 7641-7646.
Braun, U., A. Schafer, H. Walter, S. Erk, N. Romanczuk-Seiferth, L. Haddad, J. I. Schweiger, O. Grimm, A. Heinz, H. Tost, A. Meyer-Lindenberg and D. S. Bassett (2015). "Dynamic reconfiguration of frontal brain networks during executive cognition in humans." Proc Natl Acad Sci U S A.
Meyer-Lindenberg, A. (2010). "From maps to mechanisms through neuroimaging of schizophrenia." Nature 468(7321): 194-202.
Uhlhaas, P. J. (2013). "Dysconnectivity, large-scale networks and neuronal dynamics in schizophrenia." Curr Opin Neurobiol 23(2): 283-290.

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

IntegraMent

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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 x 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.

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

IntegraMent

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Introduction

Personality traits show substantial heritable components (e.g. Power and Pluess, 2015). The HeiDE study is an ongoing longitudinal investigation. At baseline, in the beginning of the 1990s, it assessed demographics and lifestyle factors together with an array of personality tests (n=5,114). At follow-up, approximately ten years later, putative associations of personality dimensions with incidence of somatic disorders were investigated (e.g. Stürmer et al., 2006). Principal components factor analysis was used to identify five latent personality dimensions ("The Heidelberg Five"; e.g. Amelang et al., 2004), interpreted as emotional lability, lack of behavioral control, type-A-behavior, locus of control over disease, and psychoticism. At this follow-up, DNA from responding participants was collected via mouthwash sample and analyzed on the PsychChip (Illumina; n=2,734). This sample presents a unique opportunity to study the association of personality, genetics, and longitudinally defined phenotypes. We have therefore embarked to study common genetic variants underlying those previously identified personality dimensions.

Methods

Calculation of individual factor scores

Personality tests collected at baseline were the following: Time Urgency and Perpetual Activation Scale, State-Trait-Anger Expression-Inventory, Hostility, Exaggerated social control, Depression Scale, Sense of Coherence Scale, Optimism, Questionnaire for measuring the locus of control over diseases, Social Support-Scale, Eysenck-Personality-Inventory, and Psychoticism. Original data were re-analyzed using principal components factor analysis with varimax rotation. We used Bartlett's method to calculate individual factor scores.

Analysis of common genetic variants

We have imputed common variants (MAF 0.01) using the 1000 Genomes Phase 3 reference panel. We plan to investigate personality dimensions within a multivariate framework that accounts for association of multiple phenotypes with a SNP.

Results and discussion

Replication of latent personality dimensions

The first ten Eigenvalues of the principal components analysis were 5.08-2.26-1.45-1.17-0.99-0.84-0.79-0.70-0.68-0.64 and are thus in perfect agreement with previously reported analyses.

Genetic analyses

We will present results of our research project at the meeting.

References

Amelang, M., Hasselbach, P., and Stürmer, T. (2004) Personality, Cardiovascular Disease, and Cancer: First Results from the Heidelberg Cohort Study of the Elderly. Zeitschrift für Gesundheitsspychologie 12:102-15.

Power, R.A. and Pluess, M. (2015) Heritability estimates of the Big Five personality traits based on common genetic variants. Translational Psychiatry 5:e604; doi:10.1038/tp.2015.96.

Stürmer T, Hasselbach P, Amelang M. (2006) Personality, lifestyle, and risk of cardiovascular disease and cancer: follow-up of population based cohort. British Medical Journal 332:1359-62.

Exome sequencing of 37 multiply affected schizophrenia families provides new insights into the pathogenesis of the disorder

IntegraMent

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Schizophrenia (SCZ) is a multifactorial psychiatric disorder with a lifetime risk of ~ 1% and a heritability of about 60-80%. 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. To our knowledge, the present study is the largest study analysing multiply affected SCZ families using WES worldwide so far.

We included 37 families with at least 3 affected members each. From each family, 3-5 individuals were exome sequenced on an Illumina HiSeq 2500 and analysed using the Varbank pipeline v2.14 of the Cologne Center for Genomics (http://varbank.ccg.uni-koeln.de). We included rare (allele frequency ≤ 0.1% in the Exome Aggregation Consortium dataset) variants that were predicted to be pathogenic (Combined Annotation Dependent Depletion Score ≥ 15; cadd.gs.washington.edu) and co-segregating with the disorder.

In total, we identified 792 variants in 742 genes co-segregating with the disorder. To analyse our candidate genes further, we carry out several studies: (i) Screening our mutations in independent patient and control cohorts through international cooperations (access to more than 3,000 SCZ patients), (ii) gene-based tests, (iii) pathway- and network-analyses, (iv) screening of selected genes in fruit flies and (v) sequencing of the candidate genes in 2,500 SCZ patients and 2,500 controls. Applying statistical methods developed within IntegraMent and combining the expertise within the subprojects of IntegraMent we were able to generate an unprecedented insight into the pathogenesis of SCZ. Analyses are ongoing and will be presented at the upcoming meeting.

Therapeutic Targets for Individualized Therapy of Schizophrenia Patients

IntegraMent

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Schizophrenia is a devastating disease that arises on the background of genetic predisposition and environmental risk factors such as early life stress (ELS). There are many pieces of evidence that suggested epigenome plays an important role in neuronal plasticity and cognitive function. Previous reports suggest that histone acetylation favours long-term memory and histone deacetylase impinges memory. There are also many pieces of evidence that suggested the role of small RNAs in memory-related functions. We had previously shown that microRNA 34c play role in dementia. We know that microRNA modulate gene expression and protein factors related to cognitive function. To further this we studied the role of histone deacetylase 1 and smallRNAome role in Schizophrenia. In this study, we show that ELS-induced schizophrenia-like phenotypes correlate with a widespread increase of histone deacetylase 1 (HDAC1) expression that is linked to altered DNAmethylation.

Enrichment of genetic variants associated with clinical response to lithium in circadian clock system gene sets

IntegraMent

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Background A connection between the mechanism of action of lithium in bipolar disorder and circadian rhythms has been suggested. Nonetheless the relationship between the “clock genes“ that regulate circadian rhythms and lithium treatment response is not completely understood. Some studies, based on candidate-gene approaches have attempted to find the association of specific genes in the clock system with treatment response. However, to our knowledge there has not been a systematic pathway / enrichment analysis of clock genes in the context of the clinical response to lithium in bipolar disorder. The objective of this study is to perform a gene-based analyses and formal gene set enrichment analyses based on circadian clock system genes, using the currently available summary statistics from The International Consortium on Lithium Genetics (ConLiGen) GWAS. Methods Based on previous literature (Pizarro et al., 2013; Chen et al., 2016) and available resources (e.g. http://circadb.hogeneschlab.org/) we have generated curated gene sets related to circadian control that are grouped as ‘clock modulator (upstream) genes’, ‘core clock genes’ and ‘clock controlled (downstream) genes’. Summary statistics derived from the ConLiGen GWAS on continuous/dichotomous lithium response were used as reference. For gene-set enrichment, analyses involved the use of two softwares in order to cross-validate the results: INRICH and MAGMA, the latter being also used for gene-based analyses. Results None of the significant associations obtained in gene-based analyses survived multiple testing correction. However gene-set enrichment analyses using INRICH and MAGMA reported a significant enrichment of a set of core clock genes with respect to the dichotomous lithium response phenotype (INRICH: corrected P=0.008; MAGMA: competitive P=0.005). No enrichment was observed using the continuous lithium response as target phenotype. Discussion Our results suggest the involvement of those genes that constitute the core clock machinery in the determination of the clinical response to lithium in bipolar disorder patients. Enrichment analyses based on other methods and other psychiatric phenotypes are ongoing in order to i) further validate these findings and ii) evaluate their specificity.

BDNF genotype modulates connectivity during cognitive control in humans

IntegraMent

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Cognitive control is a functional dimension of behavior that is reported to be affected in a range of psychiatric disorders including schizophrenia. A recently established intermediate phenotype linked to the genetic risk for schizophrenia is dorsal anterior cingulate (dACC) functional connectivity with the dorsolateral prefrontal cortex (dlpfc) during cognitive control in healthy humans (Sambataro et al., 2013). The Val66Met Polymorphism of the Brain derived neurotrophic factor (BDNF) is associated with impaired neurocognitive functioning and brain morphology, modulating a range of clinical features, such as therapeutic responsiveness (Notaras et al. 2015) In this study we examined the effect of BDNF on brain physiology in 85 healthy individuals during the performance of a modified version of the Eriksen flanker task. Although there was no difference in activation patterns, carriers of the BDNF risk variant showed significantly increased connectivity between a part of the dACC involved in cognitive Control and the prefrontal cortex, namely BA9. Our results show that BDNF polymorphisms modulate mechanisms underlying cognitive control with risk allele carriers showing increased dACC- PFC coupling a pattern previously found to be associated with schizophrenia.

The inverse link between genetic risk for schizophrenia and migraine through NMDA (N-methyl-D-aspartate) receptor activation via D-serine

IntegraMent

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Schizophrenia has a considerable genetic background. Epidemiological studies suggest an inverse clinical association between schizophrenia and migraine. However, it is unclear to what extent this inverse comorbidity can be explained by genetic mechanisms or by schizophrenia-related behavioral factors. For both disorders hypotheses of glutamate N-methyl-D-aspartate (NMDA) receptor dysfunction have been developed in the past. We hypothesized that both conditions share common genetic factors with inverse effects, primary in the glutamatergic system and genes involved in NMDA activation. Data from the population based Study of Health in Pomerania (N=3973) were used. Based on the results from the recent genome-wide association study for schizophrenia, we calculated polygenic scores (PRS) for subsets of SNPs with different p-value cutoffs and for biological subentities. These scores were tested for an association of distinct biological pathways with migraine. The PRS for schizophrenia was inversely associated with migraine in our sample. This association was exclusively based on the genome-wide hits and on single nucleotide polymorphisms near or within genes encoding proteins involved in glutamatergic neurotransmission. This association could be attributed to a single intronic variant rs4523957 in SRR encoding serine-racemase. Additional expression quantitative trait loci analyses of functional variants in SRR and gene-bygene interaction analyses further supported the validity of this finding. SRR represents the rate limiting enzyme for the synthesis of D-serine, an important co-agonist of the NMDA receptor. According to our results, a decreased versus increased activation of NMDA receptors may play a role in the etiology of schizophrenia, as well as in migraine.

Genome-wide association study of Borderline Personality Disorder reveals genetic overlap with Bipolar Disorder and Schizophrenia

IntegraMent

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Background:Borderline personality disorder (BPD) is characterized by mood lability and impulsivity – symptoms which overlap with symptoms of Bipolar Disorder (BD) – a disorder showing a substantial comorbidity. Research suggests that its etiology involves both environmental and genetic factors. Formal genetic studies indicate a heritability of up to 65%. However, to date genetic research into BPD has been limited to candidate gene studies, and no case-control genome-wide association study (GWAS) has yet been performed. Systematic genome-wide screening for BPD personality features has been performed in individuals from the general population. Here, we present the first case-control GWAS of BPD, which was performed in one of the largest BPD patients samples worldwide. Given the heritability estimates for BPD, no significant single marker results were expected. Rather, we were interested in findings pointing to genes, gene-sets, and potential overlap with other psychiatric disorders.

Methods: GWAS was performed in 1,034 BPD patients and 1,545 controls recruited at four German academic institutions (Mannheim, Berlin, Mainz, Munich). After quality control and imputation, association was tested under an additive logistic regression model using PLINK and the derived principal components as covariates. Gene-based tests were performed using VEGAS and MAGMA. Gene set analyses were performed with GSEA for GWAS using GO. Further gene set analyses are currently being performed. The LD regression score method was used to calculate genetic overlap between BPD, BD, and Schizophrenia (SCZ).

Results: The top hit of the SNP-based analysis was Developmental Pluripotency Associated 3 (DPPA3, p=1.65x10-7). The top hit of the gene-based analysis was Plakophilin4 (PKP4) which reached genome-wide significance using MAGMA (p=5.26x10-7). The gene set analysis also yielded a significant finding after correction for multiple testing, i.e., exocytosis (GO:0006887; p=0.001). The genetic correlation between BPD and BD was rg=0.34 (p=4.37x10-5), and that between BPD and SCZ was rg=0.28 (p=2.99x10-3).

Discussion: The present study is the first case-control GWAS of BPD. As expected, no significant association was found with any single marker or gene. The top SNP was in the gene DPPA3, which is implicated in epigenetic mechanisms. The top gene of the gene-based test – PKP4 – was also one of the top hits of the single marker analysis. PKP4 is involved in the regulation of cell adhesion and cytoskeletal organization, processes which have been linked to BD and SCZ. The most promising gene of the previously reported GWAS on BPD personality features - SERINC5 - showed nominally significant association. Previous research has implicated the top hit of the gene set analysis in the molecular mechanisms of BD and SCZ, and may now represent a promising starting point for further research into BPD. The most interesting finding of the present study was the genetic overlap between BPD and BD as well SCZ. Our study is the first to demonstrate on the genetic level that BPD is not a discrete entity but overlaps with major psychoses not only on the clinical level. Future studies are warranted to determine commonalities and specificities.

Network-based stratification of schizophrenia patients using rare variants

IntegraMent

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Schizophrenia is a complex disease with multiple known subtypes, including different phenotypic features like periodic catatonia (movement disorder) or cataphrenia (formal thought and speech disorder). Although, many genetic features of schizophrenia are already identified. Yet the genetic or molecular heterogeneity of patients is the reason, why it is difficult to subtype patients solely on the molecular level. Also the typically hundreds of variants per patient are usually not identical. Interestingly most mutations located on different genes may act on a similar pathway, e.g. closeby in an interaction network. Here, we aim to develop a novel method to integrate genomic mutations with gene networks. Therefore, we used rare variations identified in exome data of multiple schizophrenia affected patients to investigate 1) common pathway regulation and 2) subgrouping of patients on the pathway level into different genetic subtypes. In the first step, we mapped the variations for each patient to a known protein interaction network and smoothed the data via random walk kernel. This allows to propagate the influence of each mutation onto its network neighbours. At present, we are working on a clustering method to group patients with mutations in similar network regions together. In this process an overlay of the smoothed networks will be generated to identify small subnetworks (pathways) with similar variant profiles. Next step is to extend our method for genome-wide SNP genotyping data of various diseases to enable better disease prognostics and help to detect new subtype specific drug targets for developing new patient specific treatments.

Association between Neuropeptide Y Receptor Y2 (NPY2R) Promoter Variant rs6857715 and Major Depressive Disorder

IntegraMent, SysMedAlcoholism

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Stress increases risk for major depressive disorder (MDD), overeating, and alcohol dependence (AD). The Neuropeptide Y system is one of the best known modulators of the stress response, and some of its effects are mediated via the neuropeptide Y receptor Y2 (NPY2R). The functional NPY2R variant rs6857715 (C-599T) has been implicated in both obesity and AD but with opposing alleles. The present study explored whether rs6857715 is also associated with MDD. Analysis of the overall sample (595 MDD cases; 1295 controls) revealed an association with the AD risk allele C (P=0.020, odds ratio (OR)[C-allele]=1.18). The association remained significant after excluding MDD patients with: AD/alcohol abuse (P=0.038, OR[C-allele]=1.18); increased weight/appetite (P=0.006, OR[C-allele]=1.23); or both (P=0.008, OR[C-allele]=1.25). The present findings suggest that the NPY2R rs6857715 C-allele makes a genuine contribution to MDD.

A stochastic model relates responses to bistable stimuli to underlying neuronal processes

PsychoSys

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Viewing of ambiguous stimuli can lead to bistable perception alternating between the possible percepts. The respective response patterns show differences between schizophrenia patients and healthy controls [1,2]. At the same time, these patterns show similarities with spiking patterns of dopaminergic cells [3] that may be related to schizophrenia sprectrum disorders. Specifically, oscillatory behavior [4] with single percept changes occurs during continuous viewing of ambiguous stimuli, and stable periods followed by bursts of percept changes is observed during intermittent viewing of ambiguous stimuli.
Therefore, we propose a stochastic model that provides a link between the observed response patterns and potential underlying neuronal processes. To that end, we first develop a Hidden Markov Model that captures the observed group difference by describing switches between stable and unstable states in the intermittent presentation and using only one state in continuous presentation. Second, the model is embedded into a hierarchical model that describes potential underlying neuronal activity as difference between two competing neuronal populations [5]. This activity is assumed to generate switching between the percepts and between stable and unstable states with similar mechanisms on different neuronal levels. With only five parameters, the model can be fitted closely to a variety of response patterns and reflects the group differences between healthy controls and schizophrenia patients.

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[1] Schmack et al. (2013) J Neurosci
[2] Schmack et al. (2015) Schizophr Res Cog
[3] Bingmer et al. (2011) J Neurosci Methods
[4] Brascamp et al. (2009) J Vision
[5] Gigante et al. (2009) Comp Biology

Influence of habitual negative affect on processing of negative facial stimuli in alcoholic patients

SysMedAlcoholism

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Introduction Neuropsychological studies reported decoding deficits of emotional facial expressions in alcohol-dependent patients (ADP). Here, habitual negative affect (hNA; i.e. general tendency of experiencing negative affects such as short temper, tension, anxiety) could be one of the basic moderators, which has been associated with perception biases. Previous neuroimaging studies found altered neural activation in prefrontal and limbic brain areas during the processing of emotional facial stimuli in ADP. However, studies on the influence of hNA on neural activation during emotion processing in ADP are lacking and thus constitute the rational of this fMRI study. Methods Using a modified Hariri Faces- Paradigm, neural activation during the presentation of negative facial stimuli and neutral shapes was conducted via 3T MRI in 50 detoxified ADP and 50 matched healthy controls (HC). Habitual positive and negative affect were assessed with the PANAS questionnaire. Results Increased neural activation (contrast “aversive faces vs. neutral shapes“) was found in right OFC (BA10/11) and right hippocampus (BA28) in ADP compared to HC. Individual hNA augmented this observed activation differences between both groups. While HC showed significant interactions between high hNA and reduced bilateral functional hippocampus (BA 28) and right insula activations, ADP displayed high hNA interacting with heightened neural activation in right hippocampus (BA28). No significant neural effects were observed for habitual positive affect. Discussion According to our findings, habitual negative affect mediates functional activation patterns in brain areas involved in emotional memory formation during the processing of negative facial stimuli in both ADP and HC. Thus, habitual negative affect indeed seems to act i) as a basic moderating factor in emotional processes and ii) as an indicator of altered neural representation of a relevant personality trait in alcohol addiction.

Analysis of tissue specific genetically determined fraction of gene expression in alcohol dependent patients

SysMedAlcoholism

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Multiple clinical and genetic risk factors are involved in development of alcohol dependence (AD), e.g. activation of particular brain structures as the anterior cingulate cortex (ACC), which has repeatedly been implicated in AD.
On the other hand, alcohol use can affect functioning of different organs in heterogeneous ways, in particular that of hepatic cells, which are involved in alcohol metabolism and can thus modulate risk of developing AD. One way how such changes in an organism could be caused is by changes in amount of expressed gene products.
Recent advances in method development have enabled researchers to analyze the genetically determined fraction of gene expression for its association with clinical phenotypes. We performed this kind of analysis using models specifically trained for transcripts present in liver and/or brain (ACC).
Genome wide genotype data of a sample of 1.333 German AD patients and 2168 population based controls were imputed using 1000 genomes EUR reference sample. Based on these data transcription levels of respective genes were estimated applying the PrediXcan framework proposed by Gamazon et al. (2015) and using regression weights obtained from http://hakyimlab.org/predictdb. Resulting transcription levels were tested for association with AD using a logistic regression modelling approach.
No genome wide significant findings were obtained for single genes. Throughout all considered genes (n[ACC]=8013, n[liver]=7931) an enrichment of many small signals seems to be present in the ACC (λ=1.06). In contrast to our expectations no such effect is apparent for liver related genes in our sample (λ=0.99). This latter finding may be due to heterogeneity in sample recruitment or small sample size.

Generation and neuronal differentiation of induced pluripotent stem cells from „humanized“ mice carrying the respective human OPRM1 A118G alleles

SysMedAlcoholism

Presenting Author: Patrick Schloss

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Opioid drugs play important roles in treatment of pain, but also in the development and treatment of drug abuse. The mu opioid receptor is the primary site of action for many opioids, including morphine, heroin, fentanyl, and methadone. By sequencing DNA from 113 former heroin addicts in methadone maintenance and 39 not-addicted individuals, five different single-nucleotide polymorphisms (SNPs) in the coding region of the mu opioid receptor gene had been identified. The most prevalent SNP (allelic frequency about 10% in that study) is a nucleotide substitution at position 118 (A118G), predicting an amino acid change at a putative N-glycosylation site, which is thought to be a major determinant of striatal dopamine responses to alcohol and to be Implicated in treatment response to naltrexone in alcoholics. Moreover, the loss of Loss of N-glycosylation site has functional consequences such as the binding of ß-endorphin and the agonist-induced activation of G-protein-coupled receptors in the A118G variant is threefold higher as compared to the A118A variant. To better understand the role of OPRM1 A118G variation on alcohol dependent neuronal plasticity at the cellular and molecular level we generated humanized mice carrying the respective human OPRM1 A118G alleles. By transduction of the respective mouse embryonic fibroblasts with viral transfer of reprogramming transcription factors we then have generated 5 different clonal induced pluripotent mouse stem cell (mIPS) lines from the humanized mouse lines each, carrying the huOPRM1-118AA and huOPRM1-118GG gene, respectively. These 118AA and 118GG mIPSC are now differentiated into neurons with a defined pharmacology in order to study the impact of acute and long term alcohol on the expression and function of proteins implicated in dopaminergic and glutamatergic neurotransmission.

Polygenic burden analysis of longitudinal clusters of quality of life and functioning in patients with severe mental illness

Presenting Author: Fanny Aldinger

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Background Psychiatric illnesses such as bipolar disorder, schizophrenia and schizoaffective disorder are severe, disabling disorders associated with decreased quality of life (QOL) and functioning. In this study we aim to characterize patients with good and poor outcomes according to QOL and functioning scores. Using cluster analysis, we sought to identify longitudinal trajectories and investigate whether levels of QOL and functioning are associated with polygenic risk scores (PRS).

Methods Longitudinal data was used from the Clinical Research Group 241 and PsyCourse studies in Germany. Participants were phenotyped using a comprehensive battery which included data on socio-demographics, history of illness, symptomatology, QOL and functioning. Data was collected at four equidistant time points over an 18-month period. The Infinium Psycharray from Illumina was used to genotype patients. Relevant questionnaire items (i.e.QOL, functioning scores) were pre-selected and factor analysis for mixed data was

applied to identify trends in the data. Then the calculation of longitudinal trajectories and clustering was computed. This resulted in the identification of three distinct subpopulations of patients. In a linear regression model we used clusters as predictive variables for PRS at 11 thresholds.

Results The dimension explaining the most variance was mainly driven by QOL scores. In a sample of 198 patients, three clusters were observed; cluster A consisted of participants with the highest average scores for QOL, cluster B including participants with the lowest average scores for QOL, and cluster C consisting of participants who had great improvement in QOL scores over the course of the longitudinal study. Significant differences were seen for work status and functioning between the clusters. In cluster B there was a trend for higher PRS. Conclusion Phenotypic data provides insight to target sufferers of severe mental illness with worse outcomes. Levels of functioning and QOL seem to be associated with PRS.

Using machine learning to build individualized prediction models of future Quality of Life in psychosis patients

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Schizophrenia (SCZ), bipolar disorder (BD) and schizoaffective disorder (SCZA) are severe, chronic mental illnesses, characterized by a marked decrease in quality of life (QoL) and functioning. QoL and psychosocial functioning are important determinants of patient satisfaction and improvement in these domains is often more important for the patients than the reduction of clinical symptoms. With the growing emphasis on personalized care in everyday clinical practice, there is an increasing need for tools that can provide individual predictions on the future course of these patient-centered domains and thus help clinicians in providing individually tailored interventions. Data on sociodemographic background, family history, current psychiatric symptoms, functioning and QoL (WHOQoL-BREF) was collected from 428 participants of an ongoing longitudinal naturalistic study. Participants were genotyped on a whole-genome SNP array and their cumulative SCZ polygenic risk (SCZ-PRS) was calculated. The importance of the baseline (T1) clinical and demographic features and SCZ-PRS in predicting 6-month (T2) general and psychological QoL was tested using linear Support Vector Machines. To ensure good generalizability the prediction algorithm was wrapped into a repeated-nested cross-validation setting. Higher T1 scores on the negative symptoms subscale of the PANSS, higher levels of T1 depression, lower level of functioning and being unemployed or having a part-time job were the most important determinants of impaired T2 general or psychological QoL (test-fold balanced accuracy 61.2% and 71.3%, respectively). The SCZ-PRSs did not play an important role in determining future QoL and thus was not included in the final prediction model. Our results indicate that prognostic tools using clinical data can potentially be used to indicate future general and psychological QoL of SCZ, BD and SCZA patients. However, the predictive accuracy requires improvement to be clinically useful.

Poster Presentations

ELSA of Systems Medicine

Patient Participation in Systems Medicine

ELSA DASYMED

Presenting Author: Sebastian Schleidgen

Sebastian Schleidgen1, Sandra Fernau1, Henrike Fleischer2, Christoph Schickhardt1, Eva Winkler1

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Background: Systems medicine (SysMed) has become a key word in biomedical research. Although it is often referred to as P4-(predictive, preventive, personalized and participatory)-medicine, it still lacks a clear definition and is open to interpretation. This conceptual lack of clarity complicates the scientific and public discourse on chances, risks and limits of SysMed and may lead to unfounded hopes. Goal: We present a sufficiently precise and widely acceptable definition of SysMed.

Methods: In a first step, PubMed was searched using the keyword “systems medicine”. A data extraction tabloid was developed putting forward a means/ends-division. Full-texts of articles containing SysMed in title or abstract were screened for definitions. Definitions were extracted; their semantic elements were assigned as either means or ends. To reduce complexity of the resulting list, summary categories were developed inductively. In a second step, we applied seven criteria for adequate definitions to these categories to derive a so-called précising definition of SysMed.

Results: We identified 185 articles containing the term SysMed in title or abstract. 66 contained a definition of SysMed. 115 ends and 108 means were found in these definitions. From these we derived the précising definition: SysMed is an approach to improve stratification in medical research (disease understanding, drug discovery) and healthcare provision by methods of systems biology (data integration, modeling, experimentation and bioinformatics).

Conclusions: It becomes clear that SysMed per se does not refer to “patient participation”. Therefore, adequate instruments of patient involvement have to be developed for contexts of SysMed application.

Trust matters – Ethical Reasons for better Availability of Guidelines and Policies about Acquiring, Storing and Processing Epigenetic Data in Systems Medicine

ELSA EDEA

Presenting Author: Katharina Viktoria Röntgen

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

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Healthcare transparency and trust in the medical system are primary objectives in health politics: they are not only ethical claims, but also have been shown to lower costs and improve treatment outcomes. Although Systems Medicine is a complex and new segment, it should therefore be in the best interest of all stakeholders involved, to improve transparency and trust during all states of development in the field. Within the scope of our project on the international practices of handling epigenetic data, we examined easy online availability of policies and guidelines, on websites of universities, autonomous institutes, companies and project consortia dealing with epigenetic data in Germany, Europe and the US. Our results clearly show that stakeholder-friendly online availability of research policies and guidelines is proportionally low up to now. Regarding the importance of internet use in the information society, the average availability rate of 29.4 % seems insufficient. It is even more inadequate considering the special needs of non-specialists, whose data are used in studies and who should benefit from research in the end. Epigenetic data or testing is rarely directly addressed at all, which is questionable, considering the current prioritization of epigenetic research in Systems Medicine. These facts are obstructive to the goals of transparency and trust, besides that there are a number of additional ethical concerns identifiable, allocated primarily in science ethics and medical ethics. Key issues are equal transfer of knowledge, data protection and informational self-determination as well as enabling participation for patients.

GenoPerspektiv: Infrastructure, Ethical, Legal and Social Aspects of High Throughput Analyses in the Clinic

ELSA GenoPerspektiv

Presenting Author: Ulrich Sax

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Introduction. Increasingly effective technological pipelines allow affordable sequencing of the human genome within hours. Other high throughput technologies are at the cusp of the clinic. Yet some fundamental questions spanning from billing to legal, social and ethical questions are not resolved yet. Methods. In addition to a qualitative survey on the general perception of health professionals, patients and other affected persons on high throughput methods we conduct a much more detailed quantitative survey on 1.000 individuals on their knowledge, attitude, hopes and fears around high throughput analyses in the clinic. Results. In our interdisciplinary project, we systematically assess the impact of selected high throughput technologies on patients, health professionals and the infrastructure. On the basis of a systematic examination of current high throughput facilities we assessed the corresponding raw data and analyzed the process from the raw data to an aggregated analysis report a physician may expect. Based on the EURAT corner points on high throughput sequencing in clinical routine we discussed several crucial privacy challenges with experts from many fields and documented the best practice and challenges of data management in several core facilities. Discussion and Outlook. Aside from the maturing pipelines from biomaterial sampling to sequencing and annotating the data, the question of how to report the data and the results to the patients and their attending physician does not seem to be as mature as terms like “personalized medicine” or even “precision medicine” imply. The following clinical decision making for example by including high throughput data in a tumor board put high demands on the staff preparing and presenting the data as well as on the physician who has to decide in a very tight time frame about the future of the patient.

What does ‘translation’ mean in systems medicine?

ELSA ModMed

Presenting Author: Regine Kollek

Regine Kollek, Imme Petersen

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‘Translational research’ is not only one of the current big buzzwords in biomedicine but also an imperative for biomedical research. With the advancement of the omics-sciences and computer assisted systems biology it became evident that the gap between the life sciences, producing vast amounts of data and new insights into pathological processes on the one hand, and clinical applications of this knowledge benefitting patients on the other, is continuously increasing. Systems medicine aims at bridging this gap through the use of iterative feedback procedures between data-driven computational research and algorithms and mathematical models derived thereof, in addition to model-driven pre-clinical and clinical investigations. However, what exactly is meant by translational research or translation in the context of Systems Medicine? Although some definitions of translation have been proposed there is no common understanding of the kind of activities belonging to such research or characterizing it. Some scholars have identified translation as a heterogeneous, multidimensional endeavor, which comprises epistemic, organizational, ethical, social, and legal aspects. To this respect, translation refers to the application of verified knowledge from bench to bedside, but also to the transfer of knowledge from one realm of epistemic and social practice to another one. In order to gain a closer, empirically grounded understanding of how translation is actually understood, we conducted interviews with researchers involved in translational research in systems medicine. We wanted to explore their conception of the term and of related practices. By doing this, we were especially interested in how researchers think about bridging the epistemic and socio-cultural gaps between the many disciplines participating in translation. Essentially, we aim for a more systematic understanding of the different epistemic and socio-technical activities and instances involved in translation.

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

ELSA SYSKON

Presenting Author: Friedhelm Meier

Peter Dabrock, Rita Schmutzler, Stefan Huster, Jürgen Wasem

SYSKON. Re-Configuration of Health and Disease. Ethical, Psycho-Social, Legal and Health-Economic Challenges of Systems Medicine

Background and objectives: 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 health care system in general. The consortium aims at developing an integrative governance strategy for dealing with the identified tasks and challenges. Structure: SYSKON comprises five subprojects: Administration (SP1, Erlangen), Ethics (SP2, Erlangen), Psycho-Social (SP3, Cologne), Law (SP4, Bochum) and Health Economics (SP5, Duisburg-Essen). First year's activities: SYSKON developed and published a concise interdisciplinary research account, established a studies platform integrating stakeholders like health insurances and patient support groups and held public events (panel discussions) and lectures. Second year's activities: Based on the 'healthy-sick'-model as a potential framework for the integration of BRCA1/2 mutation carriers in particular and genetic persons at risk in general into the healthcare system (ethical SP), SYSKON investigated the challenges of risk communication and the crucial social factors influencing the decision making process (psycho-social SP). Further, SYSKON analysed the legal situation, especially the case of the BRCA2 mutation carrier Prahl vs. Federal State of Hesse. SYSKON worked out that the jurisdiction of the different levels are comparable, but the reasons given for the judgments are varying (legal SP); pointing to the lack of a clear regulation in the German health law. The economic consequences of screening and other preventive measures in the case of BRCA1/2 mutation carriers for the budget of the statutory health insurance are calculated based on a model with about 2500 persons included (health-economic SP). Perspectives: In its third year, SYSKON will transform the results of the subprojects into a governance perspective for dealing with the ethical, psycho-social, legal and economic consequences of systems medicine.

e:Med
SYSTEMS MEDICINE

Poster Presentations

Cross-topic Issues III –
Therapy Response Prediction

Proof of concept clinical trial

Mito-PD

Presenting Author: Meike Kasten

Meike Kasten, Katja Hückelheim, Andreas Ziegler, Katja Krockenberger, Daniela Berg, Christine Klein

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This 'proof-of-concept' randomized, placebo-controlled, parallel-group, double-blind, multicentric clinical trial tests an omics-based intervention strategy. As an enhancer of mitochondrial function, coenzyme Q10 (Q10) will be administered to Parkinson disease (PD) patients with different degrees of impairment in mitochondrial dysfunction. Four groups of patients will be stratified: carriers of two mutations in the PINK1 or Parkin gene (P++), carriers of one mutation in the respective genes (P+), patients selected with an omics approach who do (Omics+) or do not (Omics-) have a mitochondrial dysfunction profile. We hypothesize a gradient of mitochondrial dysfunction between groups from P++ to Omics-, translating into a gradient of clinical benefit under the study drug. The primary endpoint of the study will be the Unified Parkinson Disease Rating Scale, motor part (UPDRS III). Secondary endpoints will be a 1) magnetic resonance spectroscopy (MRSI), 2) questionnaire results addressing quality of life, depression, and fatigue, 3) a combination of the timed up and go test, a 10m walk test and finger tapping. In both centers (Lübeck and Tübingen) large numbers of idiopathic Parkinson Disease Patients (iPD) have been recruited and will be screened to form the Omics+ and Omics- groups by genetic characteristics. The rare monogenic PD patients have already been recruited. After the main trial, patients will be invited to participate in an optional, observational trial testing vitamin K2. Vitamin K2 has been shown to rescue the phenotype in a null-mutant pink1 drosophila model. It is clinically being used for treatment of osteoporosis but has not yet been tested in humans with PD for improvement of motor function. Both trial periods will be 6 months and represent the first clinical trial based on a genetic substratification of PD patients, which may lead to a differential response to mitochondrial enhancers.

The alcohol deprivation effect model for studying relapse behaviour

SysMedAlcoholism

Presenting Author: Valentina Vengeliene

Valentina Vengeliene, Hamid R Noori, Rainer Spanagel

Institute of Psychopharmacology, Central Institute of Mental Health, Faculty of Medicine Mannheim, Heidelberg University, Germany

Numerous studies in the preclinical alcohol research field show that pharmacological interventions and many other manipulations can influence alcohol consumption in a free choice paradigm in rats. These studies provide a measure of the total amount of alcohol consumed per day, but do not offer information on the drinking patterns within this period of measurement. Here we used a novel drinkometer system and methods used to analyse multiscale statistical dynamics of complex systems in order to characterize transitions between baseline and relapse-like drinking phases and to study treatment effects on relapse-like behaviour. Our data show that development of drinking behaviour undergoes critical phase transitions. Under baseline conditions, voluntary alcohol consumption in rats can be expressed as characteristic oscillations that follow diurnal activity and differ in their amplitude and frequency, depending on the ethanol concentration. This diurnal drinking rhythmicity is altered during a relapse condition, measured as an increased ethanol drinking frequency demonstrating that the deprivation phase may be a crucial component in the development of addictive behaviour. Pharmacological and other manipulations during this period interfere with either drinking frequency or the amount of ethanol consumed during a drinking approach. Intensive longitudinal datasets that derive from our drinkometer system and new multiscale statistical analysis methods provide a much deeper insight into experimental manipulation of drinking behaviour and enables us to observe progression of drinking behaviour in a stage-by-stage fashion.

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

SysINFLAME

Presenting Author: Ateequr Rehman

Ateequr Rehman (1), Konrad Aden(1,2), Wei Hung Pang(1), Richa Bharti(1), Berenice Brandt(2), Johannes Bethge(2), Susanna Nikolaus(2), Oltmann Schroeder(1), Stefan Schreiber(1,2) and Philip Rosenstiel(1)

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Background: Immune modulating recombinant antibodies (such as anti TNF antibodies) are the most effective therapies for a broad and heterogeneous group of disease including rheumatoid arthritis and inflammatory bowel disease. Pathogenesis of these diseases is argued around microbial driven activation of immune cascade and cytokine imbalance; however impact of such targeted cytokine blockade on intestinal microbial communities is poorly understood. Aim: This study aims to determine the impact of biological therapies on microbiota in patient cohort from intestinal and non intestinal diseases. Method: We enrolled rheumatic and inflammatory bowel disease patients for this longitudinal study. Healthy volunteer without any known disease served as control. Fecal samples were collected on the start of therapies and after 2, 6, and 30 weeks of therapeutic interventions. Bacterial profiles were generated from Fecal DNA by sequencing 16S rRNA gene (V4 variable region) using Mieq Illumina platform. Results: Significant changes in alpha and beta diversity indices were observed after therapeutic interventions. In addition, in IBD patient groups, bacterial phylotypes from Erysipelotrichaceae, Mogibacteriaceae, Barnesiellaceae and Ruminococcaceae were observed to be restored towards healthy subject microbiota. Likewise, significantly higher inter OTUs correlation was observed in samples collected after 2, 6 and 30 weeks of therapeutic intervention. We are now investigating these therapeutic associated microbial changes in non-intestinal (rheumatic patients) diseases, results will be presented at the conference. Conclusion: Our data suggests a marked influence of biological therapies on microbial composition and structure.

Community-level modeling of gut microbial interactions in short chain fatty acid metabolism

SysINFLAME

Presenting Author: Johannes Zimmermann

Georgios Marinos, Prof. Dr. Christoph Kaleta

Research Group Medical Systems Biology Institute for Experimental Medicine Christian-Albrechts-University Kiel (UKSH Campus)

While dietary fibers escape the digestion and absorption in the small intestine, they could be fermented by microorganisms in the colon. The major fermentation products are acetate, propionate and butyrate (short chain fatty acids, SCFA) which play, besides being an energy source, an important role in regulating the host's glucose, cholesterol and fatty acid metabolism. Moreover, SCFAs influence the inflammatory response and thereby improve health in diseases such as obesity, diabetes, or colon cancer. SCFAs are part of a highly complex metabolic interaction encompassing the diet, microbiota and host energy metabolism. We developed a computational approach, called BacArena [1] that, based on genome-scale metabolic models, allows to simulate gut microbial communities and investigate their interactions. In our study, we focused on a previously published minimal microbiome [2]. Using information on microbial abundances and diet composition, BacArena was able to correctly predict changes in SCFA production between low and high fat diets. Furthermore, we extended our simulation to a wide range of human diets to investigate SCFA production patterns. Using our approach we can track SCFA production on a individual bacterial cell level and study the contribution of individual species to colonic SCFA metabolism. We address pathway analysis, key metabolic interactions and energy yields to identify key factors responsible for colonic SCFA dynamics. [1] Bauer, Zimmermann et. al - "BacArena: Individual-Based Metabolic Modeling of Heterogeneous Microbes in Complex Communities", PLOS Computational Biology submitted, 2016 [2] Becker et. al - "Human intestinal microbiota: characterization of a simplified and stable gnotobiotic rat model". Gut Microbes 2011

Modeling individual time courses of thrombopoiesis during multi-cyclic chemotherapy

HaematoOPT

Presenting Author: Markus Scholz

Yuri Kheifetz, Markus Löffler, Markus Scholz

IMISE, University of Leipzig

Thrombocytopenia, is a major dose-limiting side effect of dose-intense cancer chemotherapies but severity is heterogeneous among patients. A major challenge of precision medicine is to predict the individual course of a patient. We revised a biomathematical model of human thrombopoiesis under chemotherapy towards modelling and predicting individual therapies and time courses. Heterogeneity of patients is traced back to the heterogeneity of a few model parameters. 28 population and 12 individual parameters were estimated using dense time series of three patients treated with BEACOPP chemotherapy. We used these estimators as population parameters as well as prior values in order to fit individually 12 parameters for sparser data of selected 135 patients from the German non-Hodgkin's lymphoma trial group receiving CHOP-like chemotherapies. Individual deviations from treatment protocol were also considered. Parameter estimations incorporate information from other published studies such as osteoblasts count change during multi-cyclic chemotherapy, average dynamics of TPO, platelets and megakaryocytes after TPO infection and platelet dynamics after labeled platelets transfusions. We propose parameter settings resulting in a good agreement of the model and experimental data, population based clinical data and individual time courses. We found an optimal tradeoff between goodness of fit and overfitting for most of the patients. Some new biological mechanisms are hypothesized: a TPO-mediated regulation of megakaryocyte commitment to either endomitosis, proplatelet formation, or to dormant state. The cumulative decrease in average platelets level during multi-cyclic chemotherapy was attributed to interactions between quiescent and active stem cells compartments as well as to the accumulating injures of osteoblasts. We established a model of individual thrombopoiesis response to chemotherapy. We will exploit the predictive potential of the model in the near future.

A tool for guided therapy adaptation to control for haematotoxic side-effects of multicycle chemotherapy

HaematoOPT

Presenting Author: Markus Scholz

Yuri Kheifetz, Markus Scholz

University of Leipzig Institute for Medical Informatics, Statistics and Epidemiology

Reduced blood cells counts are a class of major dose-limiting side effects of many dose-intense cancer chemotherapies. Several counter-measures are available such as chemotherapy dose adjustments, postponement of therapy, platelet transfusions or growth factor applications. A model-based understanding of haematopoiesis under cytotoxic chemotherapy is crucial for the development of optimized strategies avoiding or ameliorating haematotoxic side-effects. There are attempts to develop bed-side tools for risk prediction and management which are based on empirical methods or simplistic pharmacometric population models. We developed comprehensive mechanistic models of human haematopoiesis under chemotherapy and growth factor applications in the past. These models are applied to improve the prediction of individual therapy courses of patients. We constructed a standalone GUI application of our individualized human thrombopoiesis model under chemotherapy allowing Bayesian prediction of further therapy courses. The tool utilizes clinical data and data from the literature as prior knowledge to guarantee that the predictions are consistent with current knowledge. The tool is intended to be usable by physicians without modelling knowledge. The user can chose specific study and patient data from a database and perform simulations and predictions thereon. Analyses of single patients or groups of patients can be performed. The tool supports visualization of individual time courses of platelets during multicycle chemotherapy as well as predictions regarding possible modifications of the therapy during the next chemotherapy cycle. We validated the predictive power of our tool on the basis of 135 patients treated with CHOP or CHOEP chemotherapy. After 3-4 cycles our predictions are highly reliable and 30-50% more precise than those provided by other tools.

Model-based optimization of G-CSF treatment

HaematoOPT

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Although the growth-factor G-CSF is widely used to prevent granulotoxic side effects of cytotoxic chemotherapies, its optimal use is still unknown since treatment outcome depends on many parameters such as dosing and timing of chemotherapies, pharmaceutical derivative of G-CSF used and individual risk factors. We propose a comprehensive model of human granulopoiesis considering cytotoxic chemotherapy, a pharmacokinetic and –dynamic model of G-CSF and G-CSF applications (Filgrastim or Pegfilgrastim) and a cell kinetic model of bone marrow granulopoiesis. Major assumptions of chemotherapy action are: proportionality of cell numbers and cell loss, delayed action of chemotherapy, drug, drug-dose and cell stage specific toxicities, no interaction of drugs and higher toxicity of drugs at the first time of application. Implemented pharmacokinetic properties of G-CSF derivatives comprise delayed absorption from subcutaneous tissue, dose-dependent bioavailability, unspecific first order elimination, specific elimination in dependence on granulocyte counts and reversible protein binding. Pegfilgrastim shows reduced bone marrow potency compared to Filgrastim. The model is established on the basis of virtually all published evidence and own clinical data bases. It explains more than 70 different therapy scenarios comprising 10 cytotoxic drugs applied in 33 different schedules. Risk groups of granulotoxicity can be explained by differences in chemotherapy toxicity parameters rather than differences in cell-kinetic parameters. Predictions are validated on scenarios not used for model building. We demonstrate how the model can be used to predict the performance of yet untested G-CSF schedules. The model is applied to optimize G-CSF schedules for a number of chemotherapies and in dependence on the individual risk of a patient.

Anti-HLA antibody signatures provide a new tool for early diagnostics of acute graft rejection after renal transplantation

e:Kid

Presenting Author: Harald Seitz

Sabrina Herrmann 1, Harald Seitz 1, Chris Bauer 2, Nina Babel, Chantip Deng-Heine, 3 Nicole Wittenbrink, Michal Or-Guil 4

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Molecules of the human leukocyte antigen (HLA) system expressed on donor cells represent the major barrier to acceptance of kidney transplants. The presence of serum anti-HLA antibodies is associated with acute antibody mediated transplant rejection and compromised long term outcome. Studies showed that anti-HLA antibodies often precede transplant rejection, but not all patients with antibodies encounter rejection or subsequent graft loss. Finding an antibody signature predictive of rejection at an early time point could help prevent imminent graft rejection and improve long-term outcome. A total of 160 kidney transplant recipients, monitored for acute rejection events in the first year post-transplantation, were analysed for the presence and specificity of anti-HLA antibodies in pre- and post-transplant sera using LabScreen Mixed antigen beads (OneLambda). For 78 patients, at least one rejection event was observed in the first year after transplantation (rejection group). 82 patients showed no adverse events (control group). When sera tested positive for anti-HLA antibodies, antibody allele specificities were determined using LabScreen Single Antigen beads (OneLambda). Analysis of pre-transplant and post-transplant data shows that anti-HLA antibodies were more frequent in patients experiencing rejection episodes. 55% of patients in the rejection group compared to 34% of patients in the control group were anti-HLA antibody positive. Comparison of antibody specificities identified in HLA positive patients revealed a set of anti-HLA antibody specificities prevailing in either the rejection or control group. Finally, we show that raw anti-HLA antibody signature data has the potential to become a novel diagnostics tool for early, pre-transplant assessment of risk of graft rejection. Machine learning and feature selection methods succeeded in extracting significant, discriminative specificities associated with rejection with a balanced predictive accuracy of about 70%.

Discovery of novel biomarkers based on spatial immune cell patterns

SYSIMIT

Presenting Author: Ralf Schönmeyer

Ralf Schönmeyer (1), Nadine Sarah Schaadt (2), Arno Schäpe (1), Victor Matvienko(1), Carolina Vanegas (1), Wilfried Gwinner (3), Jan-Hinrich Bräsen (2), Mehmet Yigitsoy (1), Nicolas Brieu (1), Günter Schmidt (1), Friedrich Feuerhake (2)

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Oncoimmunology and transplantation medicine share the medical need for robust, immune cell-based biomarkers extracted from tissue biopsies. In an interdisciplinary approach, the Tissue Phenomics methodology was applied to mine clinically annotated image data. We provide proof-of-concept that spatial distribution of immune cells provides valuable hints towards novel transplantation biomarkers. In a pilot study with 10 renal transplant patients, needle biopsies after transplantations were retrieved and two consecutive sections were stained for CD8 and dualstain CD3/CD20. Whole Slide Images (WSI) were acquired. A module for automated cell identification detects positive and negative cells for each marker. Another module for automated landmark detection enables the local alignment of WSIs. Finally, a platform prototype produces spatially aligned maps of cell densities for each cell type. The cell densities within manually annotated regions of interest and their vicinity were used as input and correlated with clinical data. We show that comprehensive quantitative data on spatial distributions of the immune cell phenotypes can be robustly produced and displayed in registered cell density maps depicting each phenotype's densities in spatial relation to anatomical structures such as renal glomerula. Testing multiple relational features, the quotient between CD20+ and CD8+ cells' mean densities in a distance of ~150 to 300 µm to the glomerula was found as a feature with a significant correlation to the individual averaged Glomerular Filtration rate loss/year. We show that the methods in place can handle the necessary amounts and complexity of data and will allow processing additional cases, stains and clinical data for integration in the setting of clinical studies. The results indicate significant potential of the Tissue Phenomics framework to identify novel predictive factors for an improved immunological understanding of renal allograft rejections.

HER2Low – Targeting the ERBB-module in HER2-low breast cancer

HER2Low

Presenting Author: Stefan Wiemann

Ulrike Korf1, Jens Timmer2, Max Hasmann3, Birgit Bossenmaier3, Tim Beißbarth4, Annalen Bleckmann4, Tobias Pukrop4, Christine Stadelmann-Nessler4, Andreas Schneeweiss5, Eva Kantelhardt6, Martina Vetter6, Stefan Wiemann1

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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), particularly EGFR and ERBB3, are frequently expressed and potent drivers of tumor progression and metastasis. Members of the ERBB-family have been established as successful targets for targeted therapies in different tumor entities, also via application of therapeutic antibodies. While the HER2 overexpressing subtype of breast cancer shows good clinical response with targeting antibodies trastuzumab and pertuzumab, several subtypes not overexpressing HER2 have few therapeutic options and poor prognosis. While HER2 is mostly not expressed there, other members of the ERBB family are. The key hypothesis of HER2Low is that a comprehensive targeting of the EGFR/ERBB receptor module by suitable combinations of targeted drugs can efficiently shut down the cancer-driving signaling properties of this module in individual tumors. Our final aim is to predict efficient drug combinations to steer personalized therapy decisions based on the proteomic profile of a tumor. Along these lines, we unravel the mechanisms therapeutic antibodies induce on downstream signaling in response to various ligands within the tumor microenvironment. Applying a Systems Medicine approach, we use experimental and modeling technologies to identify ways to optimize treatment of breast cancer patients expressing HER2 at low to moderate levels using single or combinations of therapeutic antibodies. Mathematical models are compared with quantitative data obtained from the analysis of clinical samples to validate patterns of drug response.

Dissecting MAPK/mTOR-associated Drug Sensitivity Using a Genome-Wide CRISPR Synthetic Lethality Screen in Pancreatic Neuroendocrine Tumors

MAPTor-NET

Presenting Author: Slim Khouja

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Pancreatic Neuroendocrine tumors (pNETs) represent a heterogeneous but significant group of Neuroendocrine tumors (NETs) with an annual incidence of 1 per 100,000 and a prevalence of 1–2% in all pancreatic neoplasms (Klimstra, 2007; Klöppel et al., 2004). The majority of pNETs are sporadic but they are also commonly linked to known hereditary endocrine disorders such as Multiple Endocrine Neoplasia Type 1 (MEN1) (Alexakis et al., 2004; T. Muniraj et al., 2013). Surgical resection remains the best cure for sporadic cases but a number of less invasive treatment options are available (Carter et. al., 2013). Among them are somatostatin analogs, receptor tyrosine kinase inhibitors (Sunitinib) or mTOR pathway inhibitors (Everolimus). Due to the notorious heterogeneity associated with pNETs, the efficiency and outcome of the aforementioned therapies varies considerably (Pavel, 2013). Exome sequencing and transcriptomics have recently revealed numerous alterations within both the MAPK and mTOR networks (Boora et al., 2015; Jiao et al., 2011; Jin & Du, 2015; Vandamme et al., 2015), yet a patient stratification system is still currently lacking. Cell line models of pNETs were screened in our lab for proliferation, apoptosis and pathway status under different concentrations of available drugs targeting the mTOR and/or MAPK pathways. This allowed us to quantify the sensitivity and resistance of our pNET cell lines to these inhibitors. To dissect the underlying mechanisms related to this resistance, we plan to conduct a synthetic lethality screen using a CRISPR/cas9 library targeting the whole genome (i.e. 19,050 genes). This approach will allow us to sensitize BON1 cells to Everolimus and will give insight into which genes are essential to achieve a better drug response at potentially lower inhibitor concentrations. These data will then be validated for selected candidate genes using single-gene CRISPR Knock-out and matched to the results obtained from our established pNET-specific NGS panel. This will be further used for modeling the mTOR/MAPK pathway-associated drug effects and will contribute to the ultimate goal of improving the outcome of therapies offered in the clinic by stratifying patients according to their genetic background.

Mechanistic insight into the consequences of sublethal drug doses on therapeutic responses and unwanted metastatic outgrowth of malignant melanoma

Melanoma sensitivity

Presenting Author: Dagmar Kulms

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In response to conventional therapeutic treatment malignant melanoma represent with high relapse rates coinciding with pronounced metastatic outgrowth. The present study aims to investigate the impact of lethal as well as sublethal drug doses on long term cancer cell survival and tumor relapse. First results imply that the signalling network within melanoma cells is prone to modifications upon treatment with sublethal drug doses by differentially altering the activation status of survival proteins, including NFκB, IκBα, AKT, ERK, and JNK. The new phenotype of cells being long term conditioned to sublethal drug doses, presents with newly acquired resistance only against the specific drug used for conditioning, while responses to alternative drugs remain unaffected or increase. Regarding the potential of metastatic spreading, melanoma cells conditioned to sublethal but not to lethal drug doses display a significantly stronger migration into 3D collagen matrices, being related to NFκB-dependent upregulation of MelCAM and αVβ3 integrin. Upregulation also provided evidence for an enhanced invasive potential into 3D gels through a non-covalently cross-linked solid collagen membrane. By seeding GFP-labelled melanoma spheroids into 3D dextran-based matrices we were furthermore able to monitor spheroid behaviour (cell death versus metastatic outgrowth) upon treatment with selective drugs. To gain a holistic understanding about the relevance of parameters/interactions in the signal transduction pathways of parental versus conditioned cells we have generated a novel Probabilistic Logic Network, which is able to describe the differences and to identify sensitive nodes as potential therapeutic targets.

FALCON: A Fast Algorithm for the Contextualisation of Logical Network Models

Melanoma sensitivity

Presenting Author: Philippe Lucarelli

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Mathematical modelling of regulatory networks allows the discovery of knowledge at the systems level, like the understanding how external signals produce specific cellular behaviours. Existing approaches are often computation-heavy or not intuitive in the way of exploring the model and interpreting the results biologically. FALCON is a comprehensive computational approach based on probabilistic Boolean network modelling to build and rapidly contextualise logical models of regulatory networks with biological measurements, which depicts a probabilistic description of rule-based interactions between molecules. FALCON offers multiple types of analyses including identifiability analysis, systematic knock-out and differential regulation which can be applied to numerous biological questions. For the identifiability analysis, FALCON explores for each parameter the range of possible values and determines the fitness of the model. The resulting profiles allow to determine if certain parameters are well-constrained by the measurements. Regarding the importance of the network's interaction, FALCON allows the systematic removal of every reaction in the network. The model variants are compared using the Akaike Information Criterion, which balances goodness-of-fit with model complexity. Lastly, to account for the variability between different biological contexts e.g. different cell lines, FALCON optimizes identical models in parallel for multiple series of experimental conditions. Users can analyse in parallel which parts of the regulatory networks are activate or inactive. Such findings highlight the different regulations among cell lines and might lead to the identification of specific interventions. FALCON is an alternative tool for efficient and comprehensive analyses of regulatory networks allowing the quantitative contextualisation of large networks in a very short time. It offers an interface with a large range of analyses linked to biological applications.

Compounds triggering ER stress-induced cell death in NRASmut melanoma - Can response be predicted?

Melanoma sensitivity

Presenting Author: Christian Praetorius

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NRAS mutations in melanoma occur in up to 25% of patients and are associated with poorer prognoses. Patients often have aggressive disease requiring rapid anti-tumor intervention. Treatments are currently limited to slower-acting immune checkpoint inhibitors or chemotherapy. In a phase 3 trial, the MEK inhibitor binimetinib showed activity in patients with NRAS-mutant (NRASmut) melanoma. Overall response and disease control rates were 15% and 58%, respectively. However, an overall survival benefit was not observed. Thus, there is a substantial unmet clinical need for fast-acting drugs in patients with rapidly progressing NRASmut melanoma. Accumulating data suggest that compounds triggering endoplasmic reticulum (ER) stress induce rapid melanoma cell death, in particular in combination with MAPK (RAF-MEK-ERK) pathway inhibitors. We previously reported that the BRAF inhibitor vemurafenib induces both ER stress and inhibition of the MAPK pathway in BRAF-mutant melanoma. ER stress induction appeared to be an off-target effect of vemurafenib that remarkably enhances its pro-apoptotic activity. NRAS-mutant metastatic melanoma cell lines, including cells isolated from patients, were treated with ER stress-inducing BRAF inhibitors in combination with MEK inhibitors. In several NRASmut melanoma cell lines tested, BRAF inhibitors significantly enhanced growth inhibition and apoptosis induced by MEK inhibitors in monolayer and spheroid culture. However, we observed heterogeneity in treatment response with resistance, MEK inhibitor sensitivity or synergism. We currently determine pre-treatment expression of key MAPK and ER stress pathway components as well as regulators of terminal autophagy and apoptosis signalling in melanoma cell lines under 2D and 3D growth conditions. Protein expression amounts, data-driven systems modelling and pattern recognition approaches will be employed to assess if treatment responses can be predicted confidently.

Fusion proteins with hexavalent TRAIL assembly for melanoma therapy

Melanoma sensitivity

Presenting Author: Martin Siegemund

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Single-chain formats of TNF-related apoptosis inducing ligand (scTRAIL) facilitate the development of tumor-associated antigen-targeted as well as non-targeted fusion proteins with hexavalent TRAIL assembly for cancer therapy, combining enhanced tumor specific activation of death receptors DR4 and DR5 with a good safety profile. To further improve the scTRAIL module towards a robust, thermostable molecule of high activity, we performed a comprehensive analysis of the minimal TNF homology domain (THD) and optimized linkers between the three TRAIL subunits. A stepwise mutagenesis of the N- and C-terminal region and the joining linkers yielded bioactive scTRAIL molecules comprising a covalent linkage of the C-terminal Val280 and the N-terminal position 122 by only two amino acid residues in combination with conservative exchanges at positions 122 and 279. The increased thermal stability and solubility of such optimized scTRAIL molecules translated into an epidermal growth factor receptor (EGFR)-targeted diabody-scTRAIL (Db-scTRAIL) format, exerting high, target-dependent apoptosis induction in tumor cell lines in vitro and potent antitumor activity in vivo. In the background of melanoma therapy, we developed a melanoma-associated chondroitin sulfate proteoglycan (MCSP)-targeted molecule scFv-Fc-scTRAIL showing antigen-specific binding and enhanced bioactivity on MCSP+ melanoma cell lines like A375, compared with non-targeted, hexavalent Fc-scTRAIL. However, similarly to Db-scTRAIL, we also engineered arrangements, peptide linkers and scTRAIL modules of scTRAIL Fc fusion proteins that can be relevant as highly bioactive universal apoptosis inducers with defined molecular composition on a variety of melanomas with unknown tumor markers. Our results illustrate that protein engineering of scTRAIL and derived hexavalent formats like Db-scTRAIL, scFv-Fc-scTRAIL or scTRAIL-Fc represents a promising strategy to develop scTRAIL fusion proteins as effective cancer therapeutics.

Integrating data, tools and infrastructure to enable efficient collaboration and management in the MultiscaleHCC consortium

Multiscale HCC

Presenting Author: Erhan Kenar

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The MultiscaleHCC consortium is based on a co-clinical trial concept, which strives to develop human treatment prediction models that leverage murine prediction models, mirroring human tumor development of advanced hepatocellular carcinoma (HCC) under anti-angiogenic therapies, specifically Sorafenib. Both human and murine arms of the trial are subjected to multiple time point multi-scale and multilayer omics measurements (genomics, transcriptomics and metabolomics) and multi-modal medical imaging (Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), and Dynamic Contrast Enhanced (DCE) Computer Tomography (CT)) before and during the course of treatment. In the underlying experiments, ranging from the sample preparations and measurements up to the final biological interpretation, data generation, integration, and management are challenging and complex tasks that have to be tackled before appropriate statistical analysis techniques can be employed. As part of the project, we developed a data and project management facility that provides the modeling of the experimental design and orchestrates the seamless interplay between the data acquisition and bioinformatics facilities. On the bioinformatics side, we established an IT infrastructure that allows for automated execution of data processing and analysis pipelines. This pipeline functionality is integrated into a web portal and can be executed on a one-click-basis. All project-related data is stored in a central data warehouse and is made accessible to all consortium members through our web portal. We present the current status of our data management and bioinformatics workflow. We exemplify its utility by showing initial results from the consortium's ongoing clinical study, specifically, how gene expression patterns induced by Sorafenib treatment are extracted from a differential analysis in an automated manner. Furthermore, we will demonstrate the next generation of automated analysis pipelines, detailing how gene-set enrichment and image analysis can be practically combined across species, by presenting a complete data set (multi-omics and multi-modality imaging) at multiple time points for an exemplary patient currently enrolled in the co-clinical trial.

Boosting Therapy Response Prediction via the efficient Re-use and Integration of available Pathway Knowledge for Patient Stratification

MultiPath, i:DSem MyPathSem

Presenting Author: Frank Kramer

Frank Kramer

Junior Research Group e:Med MultiPath, Department for Medical Statistics, University Medical Center Göttingen

Molecular biomarkers will play a major role in selecting the best therapy to fight cancer. Individualized treatment decisions and specialized drugs warrant the need to broaden the focus from singular biomarkers to pathways. While Omics technologies allow the parallel measurement of many different markers, pathway databases offer vast amounts of existing knowledge on biological networks and interactions. Our aim is to present the most relevant, meaningful and interpretable patient-specific pathways to clinicians and researchers. Thus we aim to reduce the gap between patient-centered routine documentation and ontology-driven pathway and gene annotation as well as establish a seamless data-flow from single patient data to Systems Medicine. My e:Med junior group MultiPath aims at facilitating the integration of pathway knowledge and boosting reproducible research in clinical research in general and in systems medicine in particular. MultiPath aims at easing data integration via a new generic multi-layer pathway modeling framework. The central idea is the definition of a multi-layer pathway modeling framework which offers a generic and extendable format for integrating multiple pathway types and further knowledge sources influencing these pathways. Its outstanding feature is the inclusion of procedures allowing automatic pathway transformations and their documentation. Furthermore, within our e:Med i:DSem consortia MyPathSem we are developing a tool for data integration and easy access in a clinical environment in order to link clinical information systems with patient-specific Omics data and using existing prior knowledge from public pathway and literature databases. We are developing methods to generate context-specific pathways from individual patient data and will apply and evaluate these new tools on data from colorectal and metastatic cancer.

LSD1 inhibitor HCI-2509 reduces tumor growth in vitro and in vivo – implications for a novel therapy in NSCLC?

SMOOSE

Presenting Author: Iris Macheleidt

Iris F. Macheleidt, Priya S. Dalvi, So-Young Lim, Stefan Schäfer, Margarete Odenthal, Reinhard Büttner

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Lung cancer is world-wide the leading cause of cancer related deaths. Although targeted therapies are available, the five-year survival rate is still at around 18%. Therefore, new therapies are urgently needed. Since epigenetic changes often occur during cancer formation and progression, inhibitors against various epigenetic modifiers including the Lysine Specific Demethylase 1 (LSD1) were developed. LSD1 is an epigenetic writer, containing a FAD-binding site, related to the family of monoamine-oxidases that can be inhibited by Tranylcypromine (TCP). Furthermore, LSD1 was shown to be overexpressed in NSCLC in a Tissue-Micro Array. To assess whether LSD1 inhibition can be considered as a promising novel therapeutic option, we studied the impact of LSD1 on tumor cell growth in vitro and in vivo. A wide panel of NSCLC cell lines, carrying various tumor relevant mutations and gene alterations, were treated with different LSD1 inhibitors, followed by analyses of cell viability, wound healing and invasion capacities. Here, we used four different non-reversible TCP derivates (GSK690, RN-1, OG-L002 and C76) and one reversible non-TCP derivate (HCI-2509). For in vivo studies, a transgenic KRAS G12V-driven lung cancer mouse model was established and HCI-2509 was orally administered over two different time periods. Tumor growth was determined by tumor histology. Gene expression and protein level were analyzed by quantitative rtPCR, immunohistochemistry and immunoblotting, respectively. Among the five different LSD1 inhibitors, only HCI-2509 was shown to reduce the cell growth in vitro most potently with an IC50 of 2µM. Notably, HCI-2509 demonstrated a pronounced decrease of LSD1 at protein level that was linked to an elevation of H3K4me2. In the lung cancer mouse model the tumor growth was significantly reduced by early and late phase treatments of HCI-2509. In conclusion, we suggest that treatment of NSCLC with HCI-2509 is a novel therapeutical option.

Network analysis of epigenetically controlled microRNAs in neuroblastoma

SYSMED-NB

Presenting Author: Marco Lodrini

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The importance of epigenetics in cancer biology has become evident in recent years. In neuroblastoma, a childhood cancer derived from the developing sympathetic nervous system, high-level amplification of the MYCN oncogene correlates with poor overall survival in patients. An imbalance between histone deacetylase (HDAC) and histone acetyltransferase activity can create changes in the physiological patterns and levels of protein acetylation. We and others have shown that inhibiting HDAC and MYCN activity triggers strong antitumoral effects in cellular and animal models of neuroblastoma, and several microRNAs have been identified that play important roles in neuroblastoma cell proliferation, migration, invasion and metastasis. Dissecting the microRNA network controlled by HDAC and MYCN in neuroblastoma cells has the power to identify both microRNAs and their protein-encoding RNA targets that are critical vulnerable nodes for pharmaceutical targeting in the neuroblastoma transcriptome. The BE2(C) neuroblastoma cell line was treated alone or in combination with the BET-bromodomain inhibitor, JQ1, which indirectly inhibits MYCN activity, and the pan-HDAC inhibitor, panobinostat. A series of concentrations and incubation times were applied before assessing microRNA and mRNA expression using miRNA arrays as data endpoints. The targets of each differentially regulated microRNA will bioinformatically predicted using sequence-based target prediction and integration of mRNA sequencing data. Predicted protein-coding mRNA targets will be then systematically mapped to cellular pathways from the KEGG database and the mirOB database for cancer-specific pathways involving microRNAs among other database resources. The resulting network will be used to address the complexity of epigenetic drug action and related microRNA regulation in neuroblastoma cells by systems biology modelling.

Primary sugar metabolism: an Achilles heel of MYCN-dependent tumors?

SYSMED-NB

Presenting Author: Alexander Schramm

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Enhanced conversion of glucose to lactic acid in the presence of oxygen (“aerobic glycolysis” or Warburg effect) is a common biochemical feature of cancer cells acquired during cancer formation. We previously identified the oncogene MYCN as a regulator of Hexokinase II, which is a key enzyme and the rate-limiting step of glycolysis. The MYCN gene encodes a transcription factor that is important for brain development. However, this gene is often amplified and overexpressed in various tumors, including neuroblastomas. We here determined and compared the metabolic profile of a neuroblastoma cell line, SH-EP, with inducible expression of MYCN under different nutritional conditions. Ectopic expression of MYCN rendered neuroblastoma cells susceptible to glycolysis inhibition by the glucose analogue, 2-DG and this was confirmed in additional cell lines. Metabolome analyses revealed a distinct metabolic signature induced by MYCN. Moreover, principal component analyses (PCA) of metabolic changes allowed for separation of conditions as a function of both MYCN expression and nutritional status. While MYCN status did not alter enzymatic activities of glycolytic enzymes, reduction in glucose levels coupled with elevations in select glycolytic intermediates in MYCN overexpressing cells treated with high glucose or low glutamine may be suggestive of increased utilization of glucose as carbon source to support cellular expansion. Biochemical changes in cells with MYCN overexpression cultivated in the presence of low glucose levels differed from all other experimental groups and led to identification of a signature of decreased growth and/or increased apoptosis induced by glucose starvation. Thus, our findings suggest that glucose is the most important fuel for neuroblastoma cells that overexpress MYCN and that limiting glucose availability may be an important mechanism through which growth and proliferation of neuroblastomas and other MYCN-dependent tumors may be slowed.

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

SYS-Stomach

Presenting Author: Birgit Luber and Dieter Maier

Birgit Luber (1), Simone Keller (1), Gwen Zwingenberger (1), Karolin Ebert (1), Dieter Maier (2), Birgitta Geier (2), Fabian Theis (3), Jan Hasenauer (3), Sabine Hug (3), Sabrina Krause (3), Michael Meyer-Hermann (4), Jaber Dehghany (4), Haralampos Hatzikirou (4), Axel Walch (5), Michaela Aichler (5), Florian Lordick (6), Ivonne Haffner (6)

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Progress in treatment of gastric cancer (GC) has been limited due to molecular and clinical heterogeneity. Novel drugs targeting HER2 and EGFR have shown mixed success in clinical trials. While the HER2 antibody trastuzumab has been approved for GC treatment, the EGFR antibody cetuximab failed to improve patient outcomes. The SYS-Stomach consortium investigates differences in the mode-of-action of both treatments and aims at unravelling primary and secondary resistance mechanisms. We apply systematic molecular multi-omics and cell phenotypic measurements to GC cell lines. From these we derive mechanistic and statistical models of the signalling networks, coupled to cellular phenotypes and agent-based models of gastric tumours. The models will be validated against cell culture and clinical sample derived molecular and morphological tumour characteristics based on MALDI imaging mass spectrometry, a powerful tool to investigate the distribution of molecules in tumour sample sections. Validated models will be used to predict potential response and resistance factors of EGFR- and HER2-directed treatment. These response predictors will be validated in tumour samples from GC patient cohorts treated with cetuximab or trastuzumab (clinical observational VARIANZ study). We established a link between motility-focused phenotypic properties of GC cell lines with molecular characteristics in response to cetuximab and developed a GC specific semantic network connecting EGFR signalling to the regulation of cellular motility. This semantic model has been used to inform the development of a mechanistic mathematical model for the EGFR pathway which describes the measured kinetic and dose response data obtained for cetuximab responder and non-responder cell lines. This mechanistic model is linked to the phenotypic measurements, motility and invasiveness, using a regression model. An 3D agent-based model for gastric tumour growth was developed.

Deliniating multi-omics networks of radiation sensitivity in head and neck squamous cell carcinoma.

Presenting Author: Adriana Pitea

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Patients with head and neck squamous cell carcinomas (HNSCC) treated with radiotherapy alone or in combination with chemo-/immunotherapy exhibit an overall 5-year survival rate of approximately only 50%. This is mostly attributed to radiation resistance of a subgroup of tumour cells. A previous study on patients treated with radiotherapy alone identified a genomic copy number gain of chromosome 16q24.3, containing the DNA repair gene Fanconi anemia complementation group A (FANCA), which was associated with unfavourable outcome in radiation-treated patients. With this as a starting point, we set up to validate FANCA at multiple molecular levels in an independent cohort and to delineate multi-omics networks of patient response to radiotherapy. A common approach in several studies is to use mutational and/or copy number aberration level to classify genes into cancerous or repressor. However, one cannot draw any mechanistic insights out of these studies. To overcome this limitation, we introduce an integrated multi-omics framework. Our framework will enable us to understand mechanisms of radioresistance and to discover putative oncogenes as potential therapeutic targets. To depict the molecular landscape of radiotherapy treated patients on a multi-omics level, we used the HNSCC dataset available on The Cancer Genome Atlas (TCGA) portal. We want to link clinical data with copy number changes, as well as with mRNA and miRNA expression levels of the investigated HNSCC cohort on a genome-wide level. To integrate the three omics levels, we have first designed a data-driven method, called miRlastic, for the identification of mRNAs targeted by microRNAs through an elastic net regression model coupled to prior knowledge of target predictions. Functional annotation of the multi-omics regulation network was achieved by a scoring approach of the local neighbourhoods in the network. To validate the copy number gain and to characterize our subset at the genome level before integration with the miRNA and mRNA levels, we want to analyse genomic copy number data together with clinical data. For this we will use copy number profiles obtained through a good-performing copy number calling method. Tumour subclonality causes different response to radiotherapy, and thus plays an important role in radioresistance. The copy number profiles available on TCGA were obtained through a method that does not account for subclonality in tumours. Therefore, we tested two other methods for copy number calling. We simulated synthetic data and examined the performance of the cancer-tailored copy number calling methods – OncoSNP and CGHCall. In a next step we want to cross-link the mRNA and miRNA levels with genomic copy number data. Our systematic multi-omics integration framework pinpoints to treatment response associated mechanisms and thus enables us to introduce novel putative radioresistance biomarkers.

The role of cell migration in cancer and transplantation

SYS-Stomach

Presenting Author: Jaber Dehghany

SYSIMIT, SYSTOMACH, Alexey Uvarovskii, Jaber Dehghany, Michael Meyer-Hermann, Friedrich Feuerhake, Birgit Luber

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Cell migration has a central role in physiological and pathological processes. In particular, we are interested in the dynamics collective migration and the corresponding emergence phenomena using mathematical modelling. This is a common denominator in two different e:Med funded projects SYSIMIT and SYSTOMACH. In first case, we focus on understanding B-cell migration in the context of TLO formation and its implication on the success of kidney transplantation (SYSIMIT). In the other one, we theoretically investigate the effect of EGF therapies in in vitro spreading essays of gastric tumours and extrapolate their potential success in in vivo situation (SYSTOMACH).

e:Med Project Groups Overview

Informatics & Modeling

Organization:
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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.

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

Data Security & Ethics

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The Project group *Data Security and Ethics* deals with data security, data access and ethical aspects in relation to high-throughput patient data and patient informed consent. The project group is led by Dr. Christoph Schickhardt (NCT Heidelberg, ELSA 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, relating also to patient's consent, information and withdrawal. The group also co-operates with the TMF groups *Data Security* and *Molecular Medicine* (ITQM and MolMed). Significant issues are discussed with ethical and legal experts as well as scientists in order to translate relevant ethical laws into research practice.

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

Image Processing

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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.

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

Epigenetics & Sequencing

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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 ongoing activities of the Epigenetics & Sequencing group center around the following areas: (i) Application for training e:Med PhD students and postdocs within an e:Med summer school "Sequencing analysis of epigenetic deregulation in disease". (ii) Support of initiatives to acquire additional funding that covers sequencing projects in systems medicine studies. (iii) 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. (iv) Development and application of single cell sequencing technologies within e:Med.

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: PD 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	PD Dr.	DKFZ Heidelberg		
Rohr	Karl	Prof. Dr.	Universität Heidelberg	SP 3	Modeling TMM networks in tumors
Rippe	Karsten	PD 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	Dr.	Universität Heidelberg		
Rippe	Karsten	PD Dr.	DKFZ Heidelberg	SP5	Technology development for TMM classification
Pfister	Stefan	Prof. Dr.	DKFZ Heidelberg		
Luke	Brian	Dr.	Universität Heidelberg		
Plass	Christoph	Prof. Dr.	DKFZ Heidelberg		
Rippe	Karsten	PD Dr.	DKFZ Heidelberg		
Sauter	Guido	Prof. Dr. med.	Universitätsklinikum Hamburg-Eppendorf	SP6	Clinical application of TMM analysis scheme
Rippe	Karsten	PD Dr.	DKFZ Heidelberg	SPC	Coordination

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		**I**dentification 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 ell-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	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		
Kohlbacher	Oliver	Prof.	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.	Universitätsklinikum Tübingen		
Zender	Lars	Prof.	Universitätsklinikum Tübingen		
Bitzer	Michael	Prof.	Universitätsklinikum Tübingen		
Pichler	Bernd	Prof.	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, Tissue workup and
Jäger	Dirk	Prof. Dr.	NCT Heidelberg	SP1	Histological evaluation
Eils	Roland	Prof. Dr.	DKFZ Heidelberg		High-Through-Put Data Generation and Integrated
Schlesner	Matthias	Dr.	DKFZ Heidelberg	SP2	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
Sprick	Martin	Dr.	HI-STEM - Heidelberg Institute for Stem Cell Technology and Experimental Medicine gGmbH	SP 3	microenvironment
Trumpp	Andreas	Prof. Dr.	HI-STEM		
Sprick	Martin	Dr.	HI-STEM		
Eils	Roland	Prof. Dr.	DKFZ Heidelberg		Dynamic Systems Biology Models for Pathway and Drug
Bauer	Tobias	Dr.	DKFZ Heidelberg	SP 4	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		Integrated Data and Project
Lawerenz	Christian		DKFZ Heidelberg	SP 7	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	SP 1	Mathematisches Modell der Entstehung ektopischer Lymphfollikel im Kontext von Nierentransplantationen
Schönmeyer	Ralf	Dr.	Definiens AG	SP 2	Bild- und Datenanalyse von räumlichen Immunzellmustern zur Entwicklung von neuen prognostischen Gewebemarkern
Hatzikirou	Haralampos	Dr.	Technische Universität Dresden	SP 3	Mathematisches Modell der Interaktion zwischen T- und Epithelzellen in der lymphozytären Lobulitis bei erblichem Brustkrebs
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		
August	Dietrich	-	Universitätsklinikum Freiburg		
Rodriguez	Elke	Dr.	UKSH		
Baurecht	Hansjörg	Dr.	UKSH		Monogenic and oligogenic traits as an entry port to systems medicine
Grimbacher	Bodo	Prof. Dr.	Universitätsklinikum Freiburg		
Kabesch	Michael	Prof. Dr.	Universität Regensburg	SP1	
Lieb	Wolfgang	Prof. Dr.	Institut für Epidemiologie	SP2	Kindred cohorts - a tool for systems medicine
Franke	Andre	Prof. Dr.	Universitätsklinikum Schleswig-Holstein		
Rosenstiel	Philip	Prof. Dr.	Universitätsklinikum Schleswig-Holstein		Host genetics meets microbiome - a systems approach
Baines	John	Prof. Dr.	Universitätsklinikum Schleswig-Holstein	SP3	

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

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.	PD 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.	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	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

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
Loeffler	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
Loeffler	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
Loeffler	Markus	Prof. Dr.	University Leipzig	DM	Data management
Röder	Ingo	Prof. Dr.	TU Dresden		
Loeffler	Markus	Prof. Dr.	University Leipzig	SWE	Software engineering
Röder	Ingo	Prof. Dr.	TU Dresden		

HER2Low

Targeting the ERBB-module in HER2-low breast cancer

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: Dr. Dagmar Kulms

Coordinator of subproject				Subproject	
Name	First Name	Title	Institution	Nr	Title
Kulms	Dagmar	PD Dr.	Universitätsklinikum Dresden	TP1	Validating the predictive SYSACT model under organotypic 3D conditions using TRAIL/IZI1551-derivatives and trametinib/dabrafenib
Sauter	Thomas	Prof. Dr.-Ing.	Université du Luxembourg	TP 2	Extending the SYSACT model by Boolean model based network analysis incorporating TRAIL and MEK signaling networks
Meier	Friedegund	Prof. Dr. med.	Universitätsklinikum Dresden	TP 3	Translation and clinical validation of biomarkers predicted by SYSACT
Kontermann	Roland	Prof. Dr.	Universität Stuttgart		
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	
Loeffler	Markus	Prof. Dr.	Universität Leipzig	SP 3	Toponomic Models of the architectures of lymphomas
Engelmann	Julia	Dr.	Universität Regensburg	SP 4	Identification of molecular targets for immunotherapy of lymphoma using causal modeling
Beissbarth	Tim	Prof. Dr.	Universität Göttingen	SP 5	Simulation of combination therapies
Lottaz	Lottaz	Dr.	Universität Regensburg	SP 6	LYMMML, a web-portal for interactive access to the MMML data repositories

SMART Systems Medicine of Heart Failure Coordinator: Prof. Dr. med. Titus Kühne					
Coordinator of subproject				**Subproject**	
Name	First Name	Title	Institution	Nr	Title
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
Loeffler	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		
Loeffler	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

List of e:Med
Junior Research Alliances

DeCaRe

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

Coordinator: Prof. Dr. David Hassel

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

GlioPATH

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

Coordinator: Dr. Christiane Opitz

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

MILES

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

Coordinator: Dr. Martin Sos

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

mitOmics

Identification of molecular causes of mitochondrial defects by personalised omics approaches

Coordinator: Dr. Julien Gagneur

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

PsychoSys

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

Coordinator: Dr. Simon Jacob

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

SUPR-G

Systems biology of the Unfolded Protein Response in Glioma

Coordinator: Dr. Björn Tews

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

symATRIAL

Systems Medicine of Atrial Fibrillation

Coordinator: Prof. Dr. Tanja Zeller

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

SYMBOL-HF

Systems Medicine to dissect the Biology of Heart Failure

Coordinator: Prof. Dr. Steffen Just

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

TIL-REP

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

Coordinator: Dr. Isabel Poschke

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

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