e:Medium NEWSLETTER

VOLUME 5 ▪ SPRING 2022

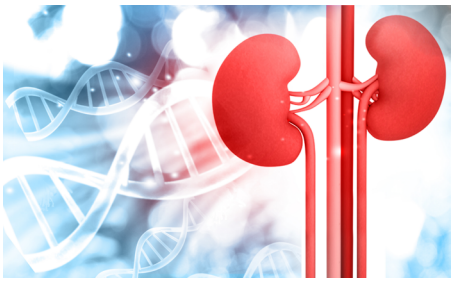
Dear Reader,

Systems medicine, the approach of our times, has the advantage of its clear view into the molecular subtleties at many relevant levels. Well over 2000 publications from e:Med projects funded by the BMBF are proving this. The second phase is in full swing, the challenging start due to the pandemic has been mastered dazzlingly. In e:Med, young inspired scientists have the chance to independently implement their project ideas at German institutions. In this issue, you will therefore read about the recent success of junior research alliances as they apply integrative multi-omics analyses on cross-disease topics in different areas, but always of systems medicine excellence.

Stay curious and enjoy reading!
Your e:Med Management Office

scOpen untangles kidney fibrosis

Improved analysis, precision in research



Fibrosis is the scarring of organ tissue. Often associated with disfunction, it is a hallmark of many chronic and metabolic diseases such as Chronic Kidney Disease (CKD). Dissecting the complex genetic and molecular interactions that lead to fibrosis is a crucial first step towards finding better diagnostics and ultimately to development of suitable therapeutic strategies against CKD. Researchers of e:Med junior research alliance Fibromap have developed a computational tool to analyse single-cell data in a more precise manner. Their tool leads to better understanding of fibrosis and uncovered a previously unknown role for gene Runx1 in fibrotic progression. An in-depth understanding of fibrotic tissue can be achieved by investigating genomic and epigenomic state of individual cells with methods such as “Single-cell Assay for Transposase Accessible Chromatin using sequencing” (scATAC-seq).

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scOPEN UNTANGLES KIDNEY FIBROSIS
Improved analysis, precision in research

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scATAC-seq data is used to determine the accessible regions of DNA in individual cells. However, the nature of the experimental protocol makes it difficult to reliably analyse and interpret the data.

Scientists of the e:Med junior research alliance Fibromap, led by Professor Ivan Costa (RWTH Aachen) therefore developed a computational tool, scOpen, which gives better estimations on open chromatin states of the cells and ultimately improves analysis and interpretation of scATAC-seq data. scOpen performed better than existing computational tools. scOpen improved downstream data analysis and led to detection of cell types and cell-regulatory changes during kidney fibrosis. When the scientists applied scOpen on data from kidney fibrosis mouse models, they revealed an unknown role of Runx1.

This gene caused differentiation of fibroblasts to myofibroblasts after kidney injury. This finding was confirmed by molecular staining in mice and overexpression assays in human fibroblast cell lines. Concurring herewith Runx1 deficiency led to a decrease in myofibroblast formation.

Understanding how fibrosis progresses in kidneys is an important step towards development of therapeutic strategies. The highly complex nature of the fibrosis, coupled with complicated experimental set-ups make it challenging to address the issue. scOpen provides a more reliable way to interpret data. The example of Runx1 in fibrotic progression proves its value. Inhibition of this gene can be used to prevent the formation of scar tissue and can thus be explored as possible therapeutic strategy for CKD patients.

Li, Z., C. Kuppe, S. Ziegler, M. Cheng, N. Kabgani, S. Menzel, M. Zenke, R. Kramann, and I. G. Costa. „Chromatin-Accessibility Estimation from Single-Cell Atac-Seq Data with Scopen.“ Nature Communications (Nov 2021)

INTESTINAL CANCER CAN FOLLOW IRRITABLE BOWEL DISEASE
Failure of DNA damage response in IBD patients

Following DNA damage, healthy cells stop dividing as a way to prevent accumulation of faulty genomic information. In inflammatory bowel disease (IBD), chronic inflammation of the intestinal mucosa is associated with a risk for developing colorectal cancer (CRC), specifically in patients with a long-standing uncontrolled disease. A collaborative study between e:Med alliances iTREAT and Try-IBD reveals how chronic inflammation impairs the normal DNA damage response and how this contributes to the risk for colorectal cancer.

IBD is an increasingly seen disease in the industrialized countries, often in young people. IBD patients suffer from diarrhoea and bloody bowel movements. X-Box binding protein 1 (XBP1) is a risk gene for IBD and has been linked to malfunctioning stress responses in intestinal epithelial cells. In normal cells, XBP1 is known to regulate stress which results from misfolded proteins. The protein governs a program which aims to resolve the stress event, e.g. by downregulating protein production. Now the scientists of the e:Med alliance iTREAT and junior research alliance Try-IBD, led by Dr. Konrad Aden (UKSH, Kiel) and Professor Philip Rosenstiel (UKSH, Kiel), respectively, showed that XBP1 may also be important for DNA damage repair in intestinal epithelial cells. They examined how XBP1 regulates epithelial DNA damage response and how its loss may lead to cancer.

Normally, cells are protected from damage to their genome by a complex DNA damage response machinery. The cells stop dividing to allow for DNA repair to take place. Thereby accumulation of faulty genomic information is prevented. The study shows that a defect of XBP1 function is associated with ongoing proliferation in spite of DNA damage. Researchers found now that XBP1 mediates DNA damage response through the p53-driven pathway. P53 is a well-known protein that functions as the guardian of the genome and as anti-tumor protein. XBP1 is shown to support p53 in its role to suppress intestinal stem cells.

The collaborative work of the e:Med alliances iTREAT and Try-IBD uncovers this previously unknown function of the gene XBP1 and provides insight into the role of chronic inflammation in intestinal cancer. Ultimately, the results may have a clinical impact for IBD patients by development of a targeted therapy.

Welz, L., ... S. Schreiber, P. Rosenstiel, and K. Aden. „Epithelial X-Box Binding Protein 1 Coordinates Tumor Protein P53-Driven DNA Damage Responses and Suppression of Intestinal Carcinogenesis.“ Gastroenterology (Sep 2021).

ONE GENE TO RULE THEM ALL
Bones, Depression, Addiction

Mental disorders are considered to be derived from malfunctions of the central nervous system. Sometimes they even appear together with further diseases. Ignoring such co-morbidities can complicate disease progression and stall treatment success. Scientists of the e:Med demonstrator alliance Target-OXY have discovered a single gene variant that is associated with alcohol addiction, depression, and bone defects. Their work brings new

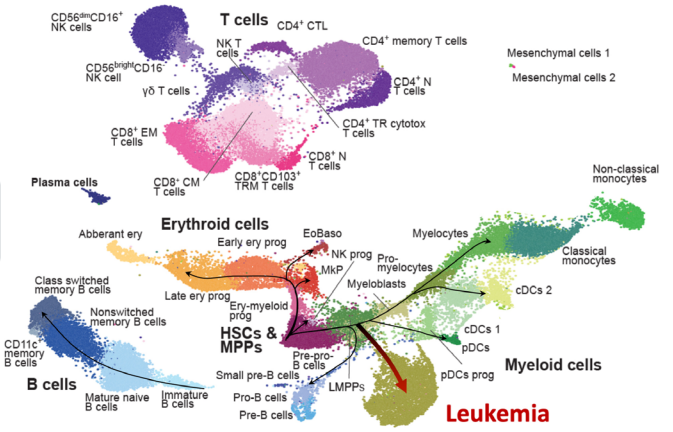
insight into the intertwined nature of mental and physical disorders thus opening up new avenues to therapy.
While searching biomarkers for alcohol abuse in the blood, the e:Med researchers of Target-OXY led by Professor Rainer Spanagel (ZI Mannheim) discovered that the enzyme neutral sphingomyelinase (NSM) has higher levels in patients than in healthy individuals. In a population-wide genetic screen, they detected that a natural variant of the gene coding for NSM is associated with alcohol consumption, depressive and anxiety states, and bone mineralisation. NSM regulates sphingomyelin metabolism in the cell. Sphingomyelin and its metabolites act as secondary messengers, functioning in a variety of cell regulatory events such as cell death, differentiation and proliferation. So, how does genetic variation of NSM affect alcohol consumption, depression, and bone defects? To understand the triangular relationship between the diseases, scientists examined what happens to mice with reduced NSM activity due to genetic alteration. These mice showed less appetite for alcohol and less anxious and depressive behaviors compared to unaltered mice. Functional MRI examination revealed increased neuronal connectivity in their brain. This may explain why these mice were less anxious and depressed. Mice with reduced NSM level show less depressive and less alcohol-dependent behavior but how healthy are their bones? To understand this, scientists measured blood osteocalcin, which is released by osteoblasts, cells responsible for bone synthesis and mineralisation. Osteocalcin levels in these mice were higher compared to normal mice. When osteocalcin was given to naïve mice, they showed reduced depressive behaviour and attenuated alcohol consumption. This observation suggests that osteocalcin has the potential to be a therapeutic option for emotional state disorder.
Thus, in this study, scientists discovered a single-gene source for a co-morbid trias of alcohol consumption, depressive state and bone defects. The link between osteocalcin signalling and emotional behavior suggests a new therapy strategy for patients with alcohol consumption in relation to emotional state disorder.

Kalinichenko, … and C. P. Muller. „Neutral Sphingomyelinase Mediates the Co-Morbidity Trias of Alcohol Abuse, Major Depression and Bone Defects.“ Mol Psychiatry (Sep 2021)

HOW DO BLOOD CELLS COME TO BE?
Single-cell proteo-genomic reference maps of human blood cells

Scientists of the e:Med junior research alliance LeukoSyStem successfully developed a way to trace the development of white blood cells from hematopoietic stem cells in detail by combining two research methods: the detection of protein molecules on the cell surface and the analysis of gene activity within the cell.
This enabled them to simultaneously capture information on thousands of individual cells from blood and bone marrow and thus clearly identify the different developmental stages of the various cell types. The scientists have published their findings, which have important implications for the diagnosis of blood cancers, in the journal Nature Immunology.
A healthy person's blood contains different types of cells: red blood cells, white blood cells, and platelets. Experts, however, make many more distinctions, especially in the case of white blood cells – the immune cells – which are composed of many different cell types. "This is very important in the diagnosis and treatment of blood cancers," says Dr. Simon Haas, head of LeukoSyStem (BIH, Charité, MDC Berlin and DKFZ, HI-STEM Heidelberg) "where the cells do not develop into functionally complete blood cells, but stop at a certain stage during their development and keep multiplying. This continues until the blood is flooded with white blood cells, the hallmark of leukemia, which literally means 'white blood.' In order to target these cells, it is necessary to have precise knowledge of them and be able to distinguish them from healthy blood cells." The use of flow cytometry analysis to discern distinct blood cells with the help of antibodies is a well-proven, fast, and inexpressive standard method. However, it lacks in precision since the currently used combinations of antibodies do not

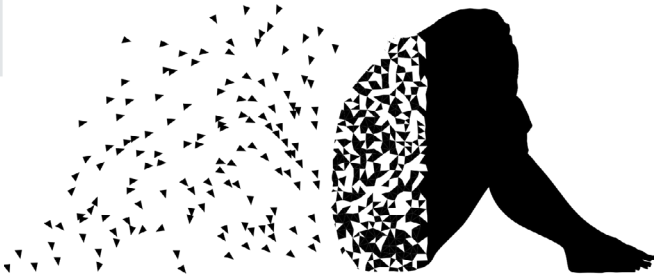
accurately discriminate all cell stages and cell types. The use of single-cell transcriptomic analysis enables a much more precise understanding of the blood and immune system as the number and composition of mRNA molecules in the cell is decisive for each cell type. “As a result, we can identify different stages of cell development, which is important when it comes to such things as more accurately diagnosing blood cancer and understanding the aging process of blood cells” stresses Haas. Yet single-cell approaches are still far too time-consuming and expensive for daily clinical use. “So we had the idea to combine single-cell analysis with surface proteome analysis, which can subsequently be used to build more powerful flow cytometry assays that can be used in clinical routines” recounts Haas. Employing these combined methods, the researchers examined hundreds of thousands of blood cells at different stages on single-cell level and thus created a highly accurate map of the development of blood system cells, both from healthy donors and leukemia patients. During their investigations, they discovered new marker proteins on the cell surface that allow for much more precise distinctions between the different cell types. The researchers used artificial intelligence (AI) to transfer the results from their single-cell analyses to cost-effective, fast and highly accurate flow cytometry assays. “We now use new combinations of antibodies suggested by AI to better identify very specific cell stages,” explains Haas. This new approach could soon prove clinically applicable in precision diagnostics of blood cancers.



Triana, S., ... L. Velten, and S. Haas. „Single-Cell Proteo-Genomic Reference Maps of the Hematopoietic System Enable the Purification and Massive Profiling of Precisely Defined Cell States.“ Nat Immunol (Dec 2021)

TELLTALES OF DEPRESSION IN OUR BLOOD
Metabolites may indicate depression

Depression is a major cause of disability worldwide. Due to its complex nature, it is difficult to explain the molecular pathways associated with depression by examining the genetic factors. e:Med junior research alliance CKDNapp chose a metabolomics approach to tackle this problem. The results of their population-wide screen for metabolites revealed laurylcarnitine to be associated with depression. This metabolite is involved in the fatty acid oxidation pathway and may provide new therapy options against depression.



The scientists of CKDNapp, led by Professor Helena Zacharias (UKSH, Kiel) focussed on examination of metabolites, i.e., small molecules, in blood samples in order to trace back to the relevant pathways. They analyzed 353 metabolites in blood samples of a cohort of 1411 people (KORA cohort—Cooperative Health Research in the Augsburg Region). Incorporated was information about their sex, age, body mass index (BMI), and intake of relevant drugs (antidiabetics, antihypertensive drugs, thyroid gland hormone drugs, anti-inflammatory and anti-rheumatic drugs, as well as anti-depressants). Depressed mood was determined by a patient questionnaire. The researchers comprehensively examined the blood of the subjects for metabolites, such as amino acids, carbohydrates, vitamins and cofactors, lipids, peptides, as well as metabolites involved in energy metabolism. Surprisingly, it was only laurylcarnitine that showed a consistent and moreover negative association with depressed mood. The lower the levels, the more depressed people were. This suggests that laurylcarnitine levels affect depression and moreover the severity of this disorder. The statistical analysis showed the same relationship between laurylcarnitine levels and depression, even when the population was stratified for sex, antidepressant use, and suicidal thoughts. To critically examine this result, the scientists measured the laurylcarnitine levels in an independent replication cohort, and received consistent results here, too. Laurylcarnitine, which belongs to the chemical class of acylcarnitines, is involved in the fatty acid oxidation pathway. Acylcarnitines facilitate the transport of fatty acids from the cytosol into the mitochondria to create energy for the cells. Previous studies had shown that some antidepressants positively affect the energy metabolism of neurons in depressed people.

This work suggests to exploit laurylcarnitine and the fatty acid oxidation pathway as novel therapeutic targets to fight depression disorders.

Zacharias, H. U., ... and K. H. Ladwig. „A Metabolome-Wide Association Study in the General Population Reveals Decreased Levels of Serum Laurylcarnitine in People with Depression.“ Mol Psychiatry (Jun 2021).

New Junior Research Alliances for an Individualized Medicine

In seven e:Med junior research alliances top young scientists are pursuing their independent research projects since 2020 implementing approaches as integrative multi-omics analyses, mechanistic metabolic modeling, and deep learning. They gain increasingly precise insight on cross-disease questions in immunology, cancer, nephrology, and neurology in the area of systems-oriented medical research. Their contribution to cooperation, knowledge transfer, and integration of IT and math in clinical training and research is significant. The e:Med junior research alliances are funded in a total of approx. 19 million euro by the BMBF.

- CKDNapp: A toolbox for monitoring and tailoring treatment of chronic kidney disease patients – a personalized systems medicine approach
- DeepLTNBC: A systemic approach to characterizing the effects of neoadjuvant chemo-therapy on triple negative breast tumors
- Fibromap: Spatial mapping of single cells in fibrotic diseases
- LeukoSyStem: Multi-scale, single-cell systems biology of leukemia stem cells in pathogenesis and therapy

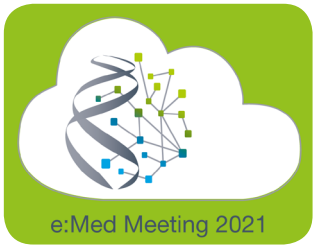
e:Med junior research alliance leaders. Top row: Stefan Florian (DeepLTNBC), Simon Haas (LeukoSyStem), Daniel Weindl (PeriNAA); bottom row: Konrad Aden (Try-IBD), Helena Zacharias (CKDNapp), Ivan G. Costa (Fibromap), Dana Westphal (MelBrainSys)

- MelBrainSys: Model-based prediction and experimental validation of novel therapeutic interventions for melanoma brain metastases
- PeriNAA: Integrative analysis of peripheral N-acetylaspartate metabolism
- Try-IBD: Multi-dimensional resolution of trypto-phan-driven immune-metabolism as a novel pathophysiological principle in inflammatory bowel disease

For more information on e:Med junior research alliances, please visit:
www.sys-med.de/en/junior-research-alliances/

To-Gather Virtually - e:Med Meeting 2021

Last September, the German systems medicine community enjoyed the virtual e:Med Systems Medicine Meeting, with its new as well as traditional aspects. The event started with piano improvisations by Michael Nickel (Berlin). Following captivating tunes, Dr. Lorna Moll (DLR PT, Bonn) from the side of the funding agency BMBF and e:Med spokesperson Dr. Matthia Karreman (DKFZ and University of Heidelberg) gave solemn opening speeches.



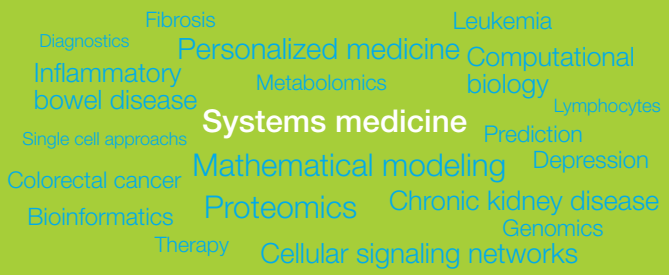
Professor Philip Rosenstiel (UKSH, Kiel) presented in the opening lecture his systems medi-cine work on the treatment of chronic inflammatory diseases and gave an outlook on the future benefits and further development. In his keynote lecture, Professor Heribert Schunkert (DHZ, Munich) explained how the assessment of coronary heart disease should include genetic alterations. Professor Julie George (University of Cologne) highlighted recent work on the molecular landscape of lung tumors with a translational focus. Besides traditional themes of the field, scientists discussed the community-proposed topics, which were integrated into the program, with interest. Through creativity and solid research, young scientists attracted attention to their posters. The community voted on twenty flash talks to pick the best. The scientific sessions followed on com-pany presentations by Illumina and Life & Brain. Among many features of the platform, community wall and video rooms called networking tables were the most engaging. Also, the community sessions Networking Fonds and Project Groups evoked strong interest from participants. For the first time, the systems medicine community discussed together in the session Perspectives of Systems Medicine, to confer on the needs and challenges of the discipline. Professor Rainer Spanagel (ZI, Mannheim) closed the event after thanking BMBF for the generous funding and our long-time spon-sors Life & Brain and Illumina for their continued support. Many applauded the success of the virtual meeting, but the desire to get together in person remains vivid. So, we are looking forward to meeting the e:Med community on-site this year: November 28-30, 2022 in Heidelberg.

e:Med News

e:Med WEBSITE

Here you find information about:
- e:Med
- all alliances and subprojects
- project groups and networking
- links to funding info, calendar, events, systems medicine news
- latest scientific results of the e:Med community

www.sys-med.de/en



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