e:Medium NEWSLETTER

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Dear reader,

Since the start of e:Med, systems medicine has moved on quite a bit. From single personalised medicine cases, biomarker detection and GWAS to development of sophisticated computational tools to analyze data and models to simulate disease processes. Bioinformatic approaches are a bigger field now and together with multi-omics technologies scientists build the basis for stratified and personalized medicine. Read here about bioinformatics tools for drug repurposing, simulating vaccinations, regulatory mechanisms of neurons, and improvements in leukemia diagnostics.

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

Faster and more sustainable

CADDIE - cancer drug repurposing tool

Drugs are usually developed against a specific disease. However, the therapeutics often have greater potential and could also be effective against other diseases that are based on a similar molecular signaling pathway. This repurposing of drugs is particularly in demand in cancer therapy to find very specific drugs in a short time. For this purpose, researchers of the e:Med consortia SyMBoD and Sys_CARE have developed the new online tool CADDIE for searching drug targets and drug repurposing candidates in cancer. CADDIE does access various gene interaction databases and can thus suggest suitable drugs for different genetic alterations.

Drug development and testing is a very long and expensive procedure. Using computational solutions for repurposing drugs that are already approved or in trials offers a fast, cost-effective and sustainable way to provide patients with therapy in a timely manner while minimizing side effects. How does one know

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FASTER AND MORE SUSTAINABLE
CADDIE: cancer drug repurposing tool

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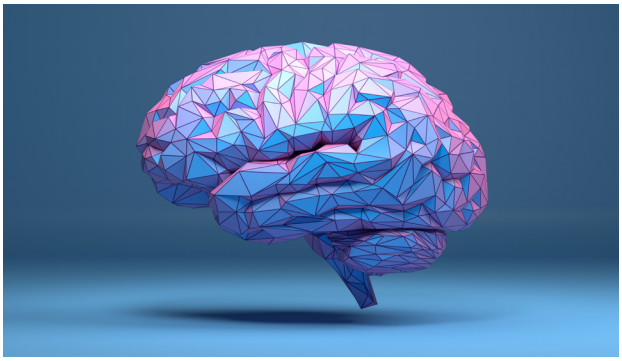
whether an existing drug is also effective for the cancer in question? The newly developed webtool CADDIE uses network pharmacology to solve this problem for the cancer driver genes of interest, i.e. the genes with mutations that can cause tumors. CADDIE suggests drugs that are known to either target the cancer driver genes directly or affect the signaling pathways they are involved in. This is done using gene-gene and gene-drug interaction databases, as well as other information on cancer driver genes, specific mutation frequencies, gene expression information, relevant genetic diseases and cancer drugs. The CADDIE webpage integrates all of this information and uses network-based algorithms to prioritize targets, find appropriate drugs, and identify potential off-targets that may lead to side effects. However, in cancer, some affected genes, such as MYC, are not directly targetable. By representing the interaction network, however, these driver genes could be indirectly targeted via their druggable interaction partners. PhD student Michael Hartung and the teams of Dr. Markus List (Technical University of Munich) and Professor Jan Baumbach (University of Hamburg) have developed the CADDIE tool especially for use in clinical research such as molecular tumor boards. They have equipped it with a user-friendly interface so that it can be easily applied by biomedical scientists. When the user enters the cancer entity and affected cancer driver genes, and selects databases and the algorithm, CADDIE suggests suitable drugs or targets. CADDIE also shows to the user approval status, actual usage, and further information about the drug. The tool generates hypotheses for personalized medicine in everyday clinical practice and sustainably exploits the potential of existing active substances.

CADDIE is available at https://exbio.wzw.tum.de/caddie/

Hartung, M., E. Anastasi, Z. M. Mamdouh, C. Nogales, H. H. H. W. Schmidt, J. Baumbach, O. Zolotareva and M. List (2022). „Cancer driver drug interaction explorer.“ Nucleic Acids Res. https://doi.org/10.1093/nar/gkac384.

NEOCORTEX
Gene regulation is becoming more specific with age

The neocortex in our brain - where complex motor functions, sensory perceptions and cognitive processes take place - contains many different types of neurons. But how do these neurons develop and how do they find their place in the brain? The e:Med junior research group DiNGS, together with American researchers, has investigated these regulatory and developmental processes in a temporally resolved manner. The scientists investigated the development of neocortical neurons at the single cell level by epigenetic and transcriptional analyses. They discovered major differences in gene regulation between neuronal development in the embryo and postnatal development.



Neurons in the neocortex differ from each other in many aspects, such as morphology, neurotransmitters, connections, or electrophysiological properties. The development of cortical neurons has often been studied. The exact regulatory mechanisms from embryonic formation to adult maturation had not yet been elucidated.

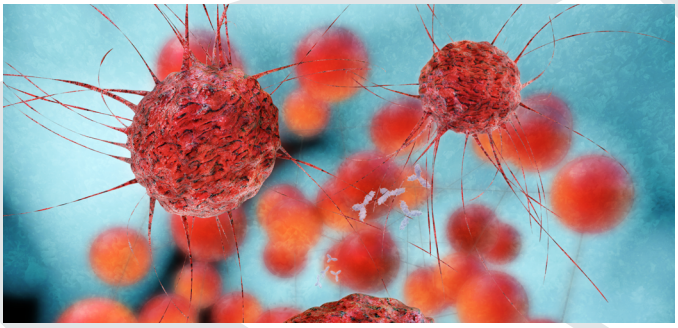
The team led by Professor Michael Ziller (University of Münster) and his international colleagues now studied individual brain cells of mice and marmosets at different times of development and in comparison between these species. They succeeded in analyzing the regulatory state of individual cell types at different developmental stages. For this purpose, they used single-cell genomic methods such as

scATAC-Seq to determine chromatin availability and RNA-seq to investigate expression status, each followed by comprehensive bioinformatics analyses.
They discovered major differences in gene regulation: in early neuronal development, neurons are controlled by widespread and evolutionarily conserved regulatory mechanisms. Mechanisms that are also known from other cells outside the brain. In later stages, as neurons matured and interconnected, regulation was more complex. It was more specific to the brain as an organ, to the brain area, and to neurons as a cell type - and also more evolutionarily divergent. This temporal shift from general to specific regulatory mechanisms was observed in all neuron types as well as in both species. The authors of the study suggest that this shift is due to evolutionary pressures. At the beginning of development, established and stable regulatory processes are important for maintaining neurons. At later stages, as neurons become specialized, more specific regulation allows more freedom to respond to environmental conditions, which may be of evolutionary advantage. These discoveries now set the stage to better understand the cell type and developmental context of disease associated genetic variation in humans, in particular schizophrenia associated genetic risk.

Yuan, W., S. Ma, J. R. Brown, K. Kim, V. Murek, L. Trastulla, A. Meissner, S. Lodato, A. S. Shetty, J. Z. Levin, J. D. Buenrostro, M. J. Ziller and P. Arlotta (2022). „Temporally divergent regulatory mechanisms govern neuronal diversification and maturation in the mouse and marmoset neocortex.“ Nat Neurosci 25: 1049–1058. DiNGS https://doi.org/10.1038/s41593-022-01123-4.

CANCER HETEROGENEITY
Accurate diagnosis by proteogenomics

Chronic lymphocytic leukemia (CLL) is a very heterogeneous type of cancer with very different clinical courses. In order to provide a prognosis and find targeted therapies, primarily genetic and transcriptional studies are already implemented. Nevertheless, there are still differences in the therapeutic course. To better understand these variances, the e:Med group SYMPATHY has now performed proteomic analyses and integrated them with genomics, transcriptomics and clinical data. Thereby the group discovered a new subtype of CLL with rapid disease progression that is detectable only at the proteomic level.
While some CLL patients manage their disease for many years with “watch and wait”, others require frequent treatment and have a poor prognosis. The genetic background of CLL is now well characterized and some targeted therapies, such as drugs that inhibit B-cell receptors, are already available. Nevertheless, the relationship between genetic variants and treatment outcomes is not well understood and the success variable. The e:Med junior research group SYMPATHY led by Professor Sascha Dietrich (University of Heidelberg & University of Düsseldorf) now used the latest in-depth mass spectrometric methods to study the proteome of clinically well characterized CLL



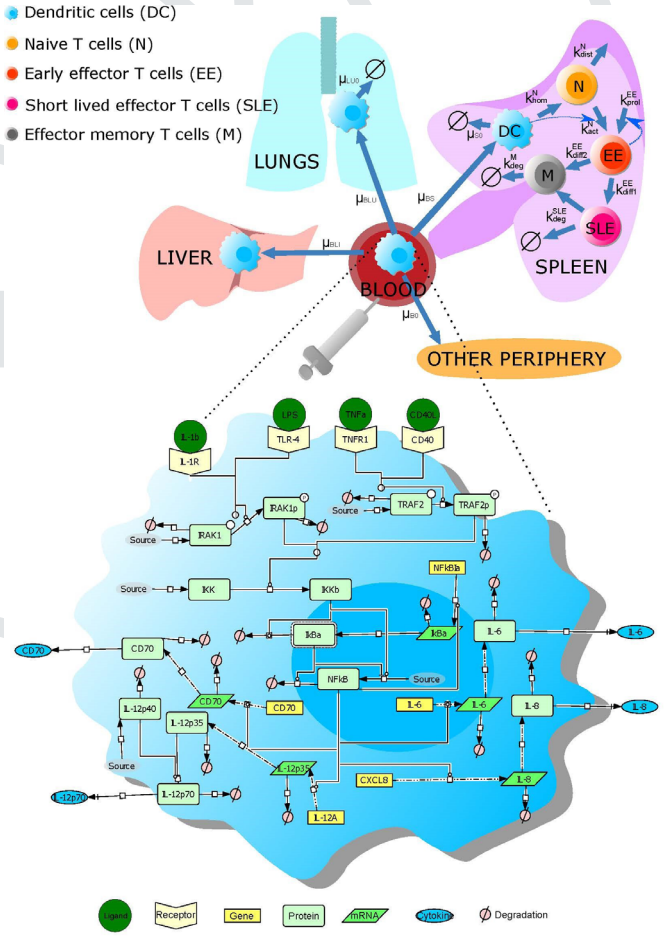
patients. For the multi-omics analysis, the researchers additionally examined the genome, transcriptome and drug response in the lab and integrated these data with the documented clinical course. The overall correlation between protein abundance and corresponding mRNA levels was low. This suggests extensive posttranslational regulation of the proteome, which is also known from other cancer entities.
Unsupervised cluster analysis of the proteomic data, where elements are assigned to different classes based on statistical parameters, segregated the patients into six subgroups. Five of these groups also showed corresponding genetic changes. However, in one proteome subgroup, no commonalities were apparent at the genetic level. At the proteome level, this new group showed large amounts of spliceosome proteins and low abundance of B-cell receptor signaling proteins and was therefore named ASB-CLL (altered splicosome, low B-cell signaling protein). Analyses also showed decreased phosphorylation of the B-cell receptor signaling pathway. A large amount of spliceosome proteins leads to altered splicing with increased exon inclusion. It is known from other studies that spliceosome protein / RNA correlation is low. This explains why ASB-CLL can only be detected at the protein level. The signature of this newly discovered group has been confirmed at multiple levels in different independent cohorts. Approximately 20% of patients are assigned to this group and show a short lymphocyte doubling

time and rapid disease progression. This multi-omics analysis updates the definition of CLL subgroups, thus optimizing individual prognosis and demonstrating how proteomics can improve stratified cancer medicine.
The data set is available to the community in a web application: https://www.dietrichlab.de/CLL_Proteomics/

Herbst, S. A., M. Vesterlund, A. J. Helmboldt, R. Jafari, I. Siavelis, M. Stahl, E. C. Schitter, N. Liebers, B. J. Brinkmann, F. Czernilofsky, T. Roider, P.-M. Bruch, M. Iskar, A. Kittai, Y. Huang, J. Lu, S. Richter, G. Mermelekas, H. M. Umer, M. Knoll, C. Kolb, A. Lenze, X. Cao, C. Österholm, L. Wahnschaffe, C. Herling, S. Scheinost, M. Ganzinger, L. Mansouri, K. Kriegsmann, M. Kriegsmann, S. Anders, M. Zapatka, G. Del Poeta, A. Zucchetto, R. Bomben, V. Gattei, P. Dreger, J. Woyach, M. Herling, C. Müller-Tidow, R. Rosenquist, S. Stilgenbauer, T. Zenz, W. Huber, E. Tausch, J. Lehtiö and S. Dietrich (2022). „Proteogenomics refines the molecular classification of chronic lymphocytic leukemia." Nat Commun 13(6226): 1–18. SYMPATHY https://doi.org/10.1038/s41467-022-33385-8.

IN SILICO
Simulating vaccination against cancer

Immunotherapies are promising approaches in personalized and targeted cancer therapy. An example of such a method is vaccination with dendritic cells (DC) presenting endogenous tumor antigens. In this procedure, the endogenous immune defense is specifically activated in such a way that the patient's own immune system destroys the tumor cells. However, since this process is enormously complex, it requires fine-tuning at many levels to function effectively and without an autoimmune response. The e:Med alliance MelAutim has now simulated such a vaccination process. This makes it possible to elucidate the molecular mechanisms of DC vaccination and to optimize these therapies.
Dendritic cells present antigens and release chemokines and cytokines, which again activate cytotoxic T-cells. With suitable antigens, these in turn are able to eliminate tumors in the patient's body. The DC-vaccination uses this mechanism by cultivating dendritic cells of the patient *ex vivo,* loading them with tumor antigens and then vaccinating the patient with these cells.



The success of such a therapy depends on many factors in the procedures in the body and ultimately on the effectiveness and number of memory T-cells. Computational modeling helps to optimize the processes *in silico* and subsequently to design experiments in a targeted manner. So far, only individual aspects of the vaccination approach have been simulated. However, the team led by Professor Julio Vera (Erlangen University Hospital) has now developed a multi-layered model that simulates DC-mediated cancer therapy in three stages: The distribution of dendritic cells in the tissue, their biochemical maturation, and their activation of CD8+ cytotoxic T-cells. The scientists calibrated the model with pre-existing experimental data. In subsequent sensitivity analyses, they identified molecules and processes that are essential for the DC-mediated T-cell response and thus for the success of the therapy. Accordingly, NF-κB regulators in particular are important for the immunogenic efficacy of DC, and cytokines such as IL-6 and IL-8 are significant for the activation of the T-cell response. Based on these findings, the scientists showed how to boost the number of memory T-cells. To do this, they simulated changes in the expression of these identified molecules, which can be influenced, for example, by transfecting mRNA or inhibitory miRNAs into DC. These simulations predicted that especially a combined change in the regulator IκBα and cytokines could increase the number of these T-cells. This model is useful as a tool for optimizing DC-based cancer therapy by identifying molecular targets and thus enabling targeted design of *in vitro* and *in vivo* experiments. It is also interesting to adapt this approach to other immunotherapies, such as CAR-T-cell therapy, to help bring personalized cancer therapies to the clinic efficiently and rapidly.

Lai, X., C. Keller, G. Santos, N. Schaft, J. Dörrie and J. Vera (2022). „Multi-Level Computational Modeling of Anti-Cancer Dendritic Cell Vaccination Utilized to Select Molecular Targets for Therapy Optimization." Frontiers in Cell and Developmental Biology 9. MelAutim https://www.frontiersin.org/article/10.3389/fcell.2021.746359.

Vera, J., X. Lai, A. Baur, M. Erdmann, S. Gupta, C. Guttà, L. Heinzerling, M. V. Heppt, P. M. Kazmierczak, M. Kunz, C. Lischer, B. M. Pützer, M. Rehm, C. Ostalecki, J. Retzlaff, S. Witt, O. Wolkenhauer and C. Berking (2022). „Melanoma 2.0. Skin cancer as a paradigm for emerging diagnostic technologies, computational modelling and artificial intelligence." Briefings Bioinf. MelAutim https://doi.org/10.1093/bib/bbac433.

Alliances for an Individualized Medicine

The e:Med module I “Alliances” is the central measure of the research and funding concept. Starting in 2019, the nine e:Med interdisciplinary research alliances each handle one joint disease-related question based on a systems medicine research approach in a large number of subprojects at different locations. Clinical working groups, high throughput-oriented teams of biomedical basic research and experts in information technology work together here.

By implementing approaches as machine learning, integrative multi omics analyses and deep learning, the alliances gain increasingly precise insight on cross-disease questions in different diseases e.g. cancer, autoimmune disorders, cardiac, renal or mental diseases as well as addictions in the area of systems-oriented medical research.

> COMMITMENT - COMorbidity Modeling via Integrative Transfer machine-learning in MENTal illness
Prof. Andreas Meyer-Lindenberg (Central Institute of mental health, Mannheim)

> InCa - A systems approach to dissect actionable heterotypic interactions of lung cancer cells with their microenvironment
Prof. Roman Thomas (University of Cologne)

> iTREAT - Development of individualized treatment paths for psoriasis and chronic inflammatory bowel diseases using systemic approaches
Prof. Philip Rosenstiel (Kiel University)

> MelAutim - Systems medicine of melanoma and autoimmunity in the context of immunotherapy
Prof. Julio Vera-González (University Hospital Erlangen)

> SASKit - Senescence-Associated Systems diagnostics Kit for cancer and stroke
Prof. Georg Fuellen (Universitätsmedizin Rostock)

> SyMBoD - System medical analysis for the personalized treatment of bone defects in patients with diabetes - animal models, biobanks and modeling
Prof. Sara Checa (Charité Berlin)

> SYMPATH - System Medicine of Pneumonia-aggravated Atherosclerosis
Prof. Martin Witzenrath (Charité Berlin)

> Sys_CARE - Systems medicine investigation of alternative splicing in Cardiac and Renal Diseases
Prof. Jan Baumbach (University of Hamburg)

> SysMedSUDs - A systems-medicine approach towards distinct and shared resilience and pathological mechanisms of substance use disorders
Prof. Rainer Spanagel (Central Institute of mental health)

>>> www.sys-med.de/en/alliances/ <<<

FINALLY FACE-TO-FACE

e:Med Meeting 2022 as in-person meeting in Heidelberg

At the end of November ‘22, after years of exclusively digital events, the e:Med community finally gathered for an in-person meeting at the DKFZ in Heidelberg. Over 230 systems medicine enthusiasts met for three days to discuss their latest research findings with their peers, to initiate new connections and renew existing ones. It was the first on-site meeting of the second e:Med funding phase and for many students the first ever – according to many new masked faces. The conference was officially opened by Dr. Nicola Scholz (BMBF), who kindly welcomed the scientists, expressing her interest in the achievements of the e:Med systems medicine community and in meeting the people behind the science. Professor Michael Boutros (DKFZ) and the e:Med speakers Professor Julie George (University of Cologne) and Professor Rainer Spanagel (ZI Mannheim) also gave warm words of welcome. Sessions spanned the spectrum of systems medicine technologies, bioinformatics, and modeling solutions to systems medicine of disease and translational approaches. Keynote speakers from the broad range of systems medicine, such as human genetics (Professor Markus Nöthen, University Bonn), individual specific networks (Professor Kristel Van Steen, KU Leuven), drug repurposing (Professor Harald Schmidt, Maastricht University) or tumor heterogeneity (Professor Stefan Pfister, DKFZ) and many more explicitly enriched the conference. Professor Bjorn Stevens (MPI Hamburg) gave “beyond the horizon” insights into climate research and modeling. Over 30 lectures on e:Med projects, 20 FlashTalks to promote the posters, a project group introduction, insights into the latest technologies from our sponsors, and a molecular disease board panel discussion characterized this inspiring meeting. The lively poster discussion at 80 posters was very well received - a part which could hardly have been realized virtually. Likewise, the integrated networking time with mocktail hour and conference dinner was very well attended and enjoyed for discussions. We thank all participants, speakers, presenters, and helpers for this inspiring meeting. See you 2023 in Berlin!

e:Med News

online Omics-Symposium

This online symposium on **Metabolomics, Lipidomics, and Proteomics 2023** is organized by the e:Med project group MS- and NMR-Based Omics. It will take place on **March 13, 2023, 12:00 - 4:30 p.m.** online via zoom. All scientists interested in these omics fields are welcome to join. Registration and further information can be found here: **www.sys-med.de/de/vernetzung/pg-ms-and-nmr-based-omics/symposium/**

Seminar Series on Modeling Disease Processes

The e:Med project group Modeling of Disease Processes organizes the online seminar series "**Modeling approaches for disease processes**". This seminar series aims to introduce, discuss and compare different mathematical modeling approaches in the field of disease modeling and is open to PhD and master students, postdocs and group leaders in the modeling field. Join us every 1st or 2nd **Wednesday** of the month, **2 p.m.** at zoom. Find further information on the website: **https://www.sys-med.de/en/networking/spalte-2/pg-modeling-of-disease-processes/online-seminar-series/**

Contributions to Public Event

Do you think your research should find its way to the public? You want to show what you are working on to young students? You want to slam your PhD project? Use the public event ‚Explore Personalized Medicine' October 09, 2023 in Berlin to make use of your science communications skills and take actively part in this public event. Show your skills, demonstrate your research in a public manner or offer a workshop. We look forward to your ideas: **info@sys-med.de**

IMPRINT

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