e:Medium NEWSLETTER

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Dear Reader,

Systems medicine is a fast growing research field. With more than 470 publications since the beginning of e:Med only three years ago, systems medicine has developed into a distinct area of research in Germany and beyond. With this newsletter, we would like to give you a few examples of what systems medicine research is about. It is not restricted to one disease or one method: The studies presented below include cancer, schizophrenia, cellular networks, allergy, and rare diseases as well as applied methods such as mathematical modeling, genotyping, proteomics, image processing and advanced statistical approaches.

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

CALCULATING CANCER

Mathematical models to predict and fight cancer

In healthy breast tissue, the presence of immune cells reflecting immunological surveillance or bystander effects during normal tissue turnover is perfectly normal. In contrast, lymphocytic lobulitis (LLO) is a recurrent immune cell pattern, characterized by lymphoid cells infiltrating lobular structures. This pattern has been associated with increased familial breast cancer risk and has been observed with enhanced frequency in non-malignant prophylactically removed breast tissue. It is difficult to distinguish LLO from common variations in immune surveillance by means of conventional microscopy. To better understand the underlying mechanisms leading to LLO, and with the intention of using this knowledge for the development of prognostic markers, e:Med scientists of the consortia SYSIMIT, around Dr. Haralampos Hatzikirou and Professor Friedrich Feuerhake, developed a mathematical model to optimize the prognostic power of immune cell infiltration in cancer. This model integrates personal patient data (menstrual cycle length, hormone status, genetic predisposition) and advanced image analysis of biopsies. The findings indicate that the immunological context, defined by immune cell density, functional orientation and spatial distribution, contains prognostic information previously not captured by conventional diagnostic approaches.

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CALCULATING CANCER
Mathematical models to predict and fight cancer

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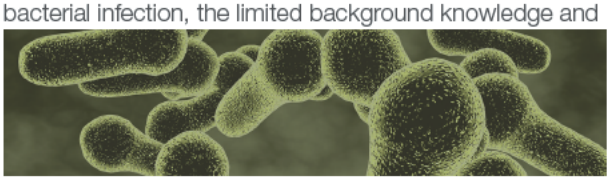
The work suggests new parameters which help to improve predictive tools for the development of cancer and have the long-term potential to improve precision of prognosis in high-risk groups, e.g. women with BRCA 1/2 mutation, regarding the risk to develop neoplasia. [1, 2]
In a further project, the scientists studied the influence of bacteria on tumor development. The phenomenon, that bacterial infections can produce efficacious anti-tumor responses, has been discovered already 200 years ago by the French physician Arsène-Hippolyte Vautier. He observed that the patient's tumors shrank when the patients additionally suffered from gas gangrene (C. perfringens) infection. However, the intense side-effects of a bacterial infection, the limited background knowledge and the low overall success rates, prevented such approaches from being employed against cancer. The scientists have now performed the first systematic study combining *in vivo* experiments and *in silico* modeling towards the mechanistic understanding of the therapeutic potential of bacterial infections against solid tumors. By means of mathematical modeling, they elucidated that bacterial infections can increase the anti-tumor response and can also change the vascularization within tumors. The model allows calculating an optimal bacterial load based on the tumor size and the corresponding immune context. This is a first step towards a personalized treatment protocol using bacterial infection. [3]



[1] Alfonso, J.C.L., Schaadt, N.S., Schönmeyer, R.,..., Feuerhake, F., Hatzikirou, H., 2016. In-silico insights on the prognostic potential of immune cell infiltration patterns in the breast lobular epithelium. Sci Rep 6, 33322. http://doi.org/10.1038/srep33322

[2] Schaadt NS, Alfonso JCL, Schönmeyer R,..., Hatzikirou H, Feuerhake F., 2017, Image analysis of immune cell patterns in the human mammary gland during the menstrual cycle refines lymphocytic lobulitis. Breast Cancer Res Treat DOI: 10.1007/s10549-017-4239-z

[3] Hatzikirou, H., Lopez Alfonso, J.C., Leschner, S., Weiss, S., Meyer-Hermann, M., 2017. Therapeutic potential of bacteria against solid tumors. Cancer Res. http://doi.org/10.1158/0008-5472.CAN-16-1621

TRACKING DOWN ALLERGIES
Decoding T cell regulation in allergies

What works differently in the immune system of allergic persons? Which immune cells can be held responsible for immune system overreaction? Scientists from Berlin, together with the e:Med consortia e:Kid around Professor Nina Babel, have now shed light on these questions.
The air around us contains an enormous number of the smallest particles of both, harmful agents and harmless substances. Our immune system faces the challenge of distinguishing between the two in order to react against dangerous agents and at the same time tolerate harmless substances. It is generally accepted that specific immunosuppressive cells (Treg) inhibit the immune response to harmless substances by blocking allergenic cells (Th2). However, in some humans, harmless pollen may cause a pathologic immune response due to excessive T cell activity, which leads on to the development of allergies. It was presumed for a long time that allergies were caused by a defect of the immunosuppressive Treg cells, not only because of methodical limitations, the evidence is missing. With the help of a new technology in this study large numbers of antigen- (allergen-) specific T cells were isolated from the blood and analyzed by e:Med scientists using specifically established methods. In this context, researchers have found that there is no difference in regulatory T cells between healthy

individuals and persons suffering from an allergy, neither quantitatively nor qualitatively. They have further shown that specific easily-soluble substances generally trigger only a reduced activation of these regulatory cells. It is precisely these substances that may lead to allergies, through the lower control of the Tregs, the allergenic Th2 cells are freer to react. Thus, in allergic patients, the regulatory T cells are fully functional; however, Th2 cells are overreacting causing allergy symptoms. It is still unclear, why Th2 cells are using this loophole in patients while they behave "normal" in healthy persons. The finding, that the degree of activity in Tregs is dependent on the antigen, can help to optimize allergy therapy by specifically activating these cells which again suppresses immune active Th2 cells.

Bacher, P., Heinrich, F., Stervbo, U., Nienen, M., Vahldieck, M., Iwert, C., Vogt, K., Kollet, J., Babel, N., ..., M., Scheffold, A., 2016. Regulatory T Cell Specificity Directs Tolerance versus Allergy against Aeroantigens in Humans. Cell 167, 1067–1078.e16. http://doi.org/10.1016/j.cell.2016.09.050

e:Med Webinar Service

Would you like to present your systems medicine research project? Or hold seminars on new software in an efficient and effective way? Try out using webinars! It's a perfect way to transfer knowledge within a short time and regardless of the location. We now offer the opportunity for all e:Med members to perform and record their own webinars. State-of-the-art technology and full support will be provided and organized by the e:Med management office in cooperation with the DKFZ department medical physics. The Webinars will be placed on our website to transfer systems medicine to the interested public. Do you have a webinar idea? If so, please contact Karin Greulich-Bode (k.greulich@dkfz.de) and visit our website:
> www.sys-med.de/en/current/webinars/

e:Med Meeting 2017

Save the date for the e:Med Meeting 2017, which will be held from **November 21 to 23** at Georg-August University **Göttingen**. We look forward to welcoming all of you to three days full of discussion, networking, and science. The meeting will take place at the ‚Alte Mensa', a newly renovated historical building in the heart of Göttingen, which offers plenty of space for talks, poster exhibitions and socializing. The program embraces diverse sessions on systems medicine, including common diseases, approaches in clinics, technologies and models, as well as European systems medicine. It also offers broad opportunities to present your research findings to the community. The meeting is free of charge, however registration is mandatory. Abstract submission and registration opens soon. Please check our website for further information:
> www.sys-med.de/de/meeting

What is hidden behind...

SYSIMIT?

Central theme is the prognostic value of immune response to cancer and allograft transplantation. Beyond current practice to microscopically describe and quantify immune infiltration, SYSIMIT aims to identify complex spatiotemporal immune cell patterns, predictive for disease course or treatment response. A key element of this novel approach is *in silico* modeling of relevant disease processes, integrating comprehensive spatial data into multiscale mathematical models, and utilizing innovative image analysis and data mining technologies to explore the full prognostic potential of biopsy images.
>>> see: Calculating cancer

mitOmics?

Uncovering the diverse molecular backgrounds of rare mitochondrial diseases by using personalized omics approaches is the research focus of mitOmics. For this purpose whole-genome sequencing, transcriptome profiling and genome-wide functional screens are combined. Integrative bioinformatics and statistical analyses are applied to indicate causative mutations and affected pathways for each patient. This knowledge enables precise personalized therapy for the individual patient. The novel developed protocols and algorithms shall be translated into clinical routine and applied as diagnostic tools.
>>> see: Nutrition supply as therapy

IntegraMent?

Identifying underlying pathways leading to neuropsychiatric disorders is the main goal of IntegraMent. New candidate genes, comorbidities and health risks are elucidated by applying genome wide sequencing methods, advanced statistical approaches and functional NMR examinations in large patient cohorts. The molecular functions of genetic mutations are analyzed using animal models and stem cells. Integrating data from diverse experimental levels allows to model disease mechanisms and brings a deeper understanding of the biological basis of psychiatric diseases and translation into patient care.
>>> see: Genes change networks

METABOLIC FINE-TUNING

Amino acids as signaling molecules: Interactions uncovered

Amino acids are recognized as essential building blocks for proteins and are abundant in nutrient rich environments. In addition, amino acids are also important signaling molecules which influence cellular and organismal metabolism and the malignancy of cancer cells. The oncogenic protein kinase mTOR (mammalian target of rapamycin) is a key player in the cellular signaling network which transduces amino acid signals and promotes cell growth. Do amino acids also target other signaling proteins to fine-tune cellular metabolism? This question is central to the project of e:Med scientists around Professor Kathrin Thedieck, Dr. Sascha Schäuble and Dr. Daryl Shanley (MAPTor-NET and GlioPATH research alliances). The scientists conducted a systems study in which they combined lab experiments with dynamic *in silico* modeling of the amino acid signaling network, as well as proteomics with text-mining analyses. They found that next to the well-known amino acid target mTOR also other signaling molecules - class I phosphatidylinositide kinases (PI3K) and the energy-sensing kinase AMPK (AMP-dependent kinase) - are activated by amino acids. Thus, the influence of amino acids is broader than previously assumed. One of the targets, AMPK, is widely considered as an mTOR antagonist as the two kinases have opposite roles in autophagy regulation. Here, the authors found that mTOR and AMPK are concomitantly active when amino acids are present, allowing active autophagy and protein synthesis at the same time. Autophagy is a cellular process in which macromolecules are degraded. Autophagy is therefore not only important for the clearance of damaged cellular components, but it also provides metabolite intermediates required for biosynthetic processes, including translation and cellular growth. The study of Dalle Pezze et al. broadens the scope of the cellular functions of amino acids and shows how to decode complex signaling networks by combined modeling and lab experiments.

Dalle Pezze, D., Ruf, S., Sonntag, A.G.,..., van Eunen, K., Tölle, R.C., Schwarz, J.J., Wiese, H., Warscheid, B., Deitersen, J., Stork, B., Fäßler, E., Schäuble, S., Hahn, U., Horvatovich, P., Shanley, D.P., Thedieck, K., 2016. A systems study reveals concurrent activation of AMPK and mTOR by amino acids. Nat Commun 7, 13254. http://doi.org/10.1038/ncomms13254

NUTRITION SUPPLY AS THERAPY

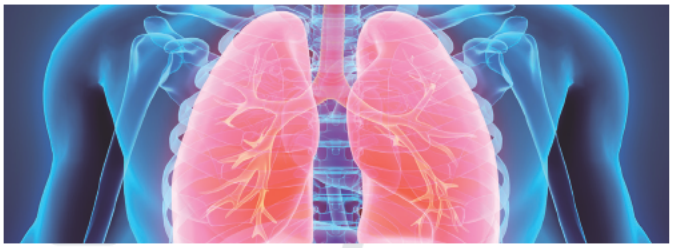
RNA building blocks for children suffering epileptic encephalopathy

Developmental disorders and epilepsy in infancy can have various causes. Novel methods such as high-throughput sequencing allow a correct diagnosis of even rare genetic diseases – but in many cases without effective medical treatment. Some genetic defects, however, affect enzymes involved in metabolic pathways. Products resulting from that pathway can be replaced by targeted administration of dietary supplements. One example for a personalized therapy approach on the grounds of a detected mutation is given in a study by scientists from Munich and Salzburg, supported by the e:Med junior research alliance mitOmics around Dr. Tobias Haack. The symptoms of already two children were effectively treated by administering a dietary supplement. Prior to the therapy, the examined children showed a severe developmental delay including epilepsy, anemia and a decline in acquired motoric skills. Siblings with equal genetic alterations died already in early childhood. Using exome-sequencing a pathogenic mutation in the CAD-Gene was detected. This CAD-gene encodes a multifunctional enzyme that plays a central role in the pyrimidine biosynthesis – building blocks for DNA, RNA or polysaccharide. Pyrimidine does not necessarily have to be newly synthesized. It can also be recycled from the RNA building block uridine, which is also available as a dietary supplement. After genetic diagnosis, the children were treated with the naturally occurring uridine, which led to immediate improvement of symptoms including missing epileptic attacks. Whereas prior to treatment the children had little capacity to interact with their environment, after about six month of treatment they were able to walk a few steps and to communicate. This enormous relief of symptoms of the otherwise often fatal disease, by simply supplementing uridine, makes CAD-defect a potential disease suitable for newborn screening.

Koch, J., Mayr, J.A., Alhaddad, B., Rauscher, C., Bierau, J., Kovacs-Nagy, R., Coene, K.L.M., Bader, I., Holzhacker, M., Prokisch, H., Venselaar, H., Wevers, R.A., Distelmaier, F., Polster, T., Leiz, S., Betzler, C., Strom, T.M., Sperl, W., Meitinger, T., Wortmann, S.B., Haack, T.B., 2017. CAD mutations and uridine-responsive epileptic encephalopathy. Brain 140, 279–286. http://doi.org/10.1093/brain/aww300

THE IMPORTANCE OF BEING GENOTYPED

Personalized medicine for small cell lung cancer



Small cell lung cancer is an aggressive type of cancer with an extremely low survival rate, since many of the patients rapidly develop resistance against chemotherapy. However, standard therapy has hardly changed over the last 40 years. Furthermore, a detailed characterization of the course of therapy of single tumors can only be carried out insufficiently, even though the disease can progress in very different, individual ways. In close cooperation with the team of Trudy Oliver from Huntsman Cancer Institute in Utah, e:Med team leader Professor Martin Sos and Professor Roman Thomas (MILES and SMOOSE) now have discovered, that for patients with a particular genetic alteration a new and very promising combination therapy can be applied. Earlier studies have shown that among most patients the tumor suppressor genes RB1 and TP53 are non-functional. In addition, in some patients the oncogene MYC is to be found overactive, which is associated with a poor prognosis. Why these tumors are particularly aggressive is not yet clear. By means of a newly developed mouse model with this exact combination of mutations the scientists from Cologne were able to detect the molecular mechanisms of tumor differentiation and study new therapies. Within a very short time the mice develop lung tumors and show a specific expression pattern of characteristic neuroendocrine markers, which the scientists have also found in human samples. Murine metastases develop quickly, which is similar to the situations in humans. This mouse model is ideal for developing the best possible therapies and subsequently provides patients with individual treatment. Tests indicate that tumors show very good response to chemotherapy, but rapidly form treatment resistances. Additional MYC inhibition (by aurora kinase inhibitors) prevents relapse and allows chemotherapy to be effective. Precisely this specific therapy may be applied in future to treat small cell lung cancer patients with high MYC expression. The study shows the importance of investigating the background of diseases in order to establish personalized therapies.

Mollaoglu, G., Guthrie, M.R., Böhm, S., ..., Peifer, M., Thomas, R.K., Gertz, J., Johnson, J.E., Gazdar, A.F., Wechsler-Reya, R.J., Sos, M.L., Oliver, T.G., 2017. MYC Drives Progression of Small Cell Lung Cancer to a Variant Neuroendocrine Subtype with Vulnerability to Aurora Kinase Inhibition. Cancer Cell. http://doi.org/10.1016/j.ccell.2016.12.005

GENES CHANGE NETWORKS

Schizophrenia risk mutations lead to instable neuronal networks

How does Schizophrenia work on the molecular level? What is the genetic impact on this disease? Up to now it was only known, that the interactions between brain regions follow different patterns and that the disease has a hereditable component. It was however not clear, which molecular and genetic implications led to these changes. Studies show that lowered activity of the glutamate receptors and the thereby hindered signaling transfer between the neurons might be important. e:Med scientists of the consortium IntegraMent with Urs Braun, Dr. Dr. Heike Tost and Professor Andreas Meyer-Lindenberg employed imaging processes and pharmacological interventions and hereby discovered that patients suffering from schizophrenia build neuronal networks with lower stability. This was traced back to an altered glutamatergic signaling transfer, which has a huge genetic impact. In this study the brain from patients and first degree relatives were examined via functional magnetic resonance tomography during performing a memory task (n-back test). It was already obvious here that the brain regions of patients communicate differently and build more labile networks compared to the control group. Interestingly, dynamic networks of the patients' relatives, which share half of the genetic risk gene load, show a similar type of aberrations. This altered network stability was intermediate between control persons and patients, which allows conclusions on a high genetic influence. In further experiments the control persons took a medication, which blocks the glutamate receptors. This induced limitation in signaling transfer led to a similar brain anomaly as previously observed within the patients. The scientists concluded that the glutamatergic receptors play a key role in building stable neuronal networks and thus in developing schizophrenia. Therefore, these neuronal dynamics are a prospective target for the development of efficient medication.

Braun, U., Schäfer, A., Bassett, D.S., ..., Erk, S., Romanczuk-Seiferth, N., Grimm, O., Geiger, L.S., Haddad, L., Otto, K., Mohnke, S., Heinz, A., Zink, M., Walter, H., Schwarz, E., Meyer-Lindenberg, A., Tost, H., 2016. Dynamic brain network reconfiguration as a potential schizophrenia genetic risk mechanism modulated by NMDA receptor function. Proc. Natl. Acad. Sci. U.S.A. 113, 12568–12573. http://doi.org/10.1073/pnas.1608819113

e:Med News

SUMMER SCHOOLS

Deep sequencing techniques are focus of the summer school **"SEquencing analysis of Epigenetic DEregulation in Disease" (SEEDED)** organized by the e:Med project group Epigenetics & Sequencing. There will be three modules comprising practical courses and interactive lectures in July and September located in Heidelberg at EMBL, DKFZ and Crowne Plaza. Interested candidates should provide an abstract about their current research and interests. Online application deadline ends on **May 24, 2017.** For further information contact Tanja Jutzi (t.jutzi@dkfz.de) or see our website:
> www.sys-med.de/seeded

The summer school **"CardiOvascular Systems MEdicine" (COME)** takes place at the UKE in Hamburg this September. The workshop integrates knowledge from epidemiology, cohort studies, bioinformatics, statistics, and molecular biology and will bridge the gap between theory and practice of systems medicine approaches. Deadline for application submission is **May 31, 2017.** Please find further information on the website:
> www.summer-school-come.de

COMMENT FUNCTION

Comment the research highlights on the e:Med Website to foster interesting dialogue and discussion.

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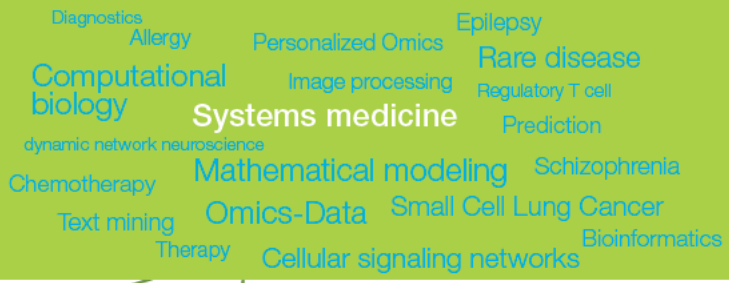
> www.sys-med.de/de/aktuelles/emed-in-den-medien/



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info@sys-med.de
www.sys-med.de

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