# e:Medium NEWSLETTER

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Dear Reader,

Systems medicine is becoming increasingly important. The 1350 publications from systems medicine projects with e:Med funding since 2014 clearly testify to this. In addition, this is evident in the growing number of translational projects that bring systems medicine knowledge into the clinic. Now further success of the e:Med projects can follow: Twenty new projects are at the start and will pick up speed in 2019/2020. We will introduce the four Demonstrators, nine Research Alliances and seven Junior Research Alliances to you in the upcoming editions of the e:Med*ium*. We look forward to welcoming new topics, ideas and faces in this second funding phase. In this e:Med*ium* you read about recent results and get an overview of the new e:Med structure.

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

## Specific Treatment of Inflammatory Bowel Disease

### Microbiome predicts treatment success

In Germany, about 320.000 people suffer from chronic inflammatory bowel disease (IBD), which is associated with chronic diarrhea, fever, pain and psychological stress. The two most common representatives for IBD are ulcerative colitis (UC) and Crohn's disease (CD). One common therapy for IBD is treatment with antibodies against immune components that slow down and control inflammation. However, these drugs, which are used for biologic therapies, do not affect all patients equally, as in some patients the symptoms persist. Compared to the intestinal microbiome of healthy people, IBD patients have a smaller variety of microorganisms in their intestinal flora.

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## SPECIFIC TREATMENT OF INFLAMMATORY BOWEL DISEASE
## Microbiome predicts treatment success

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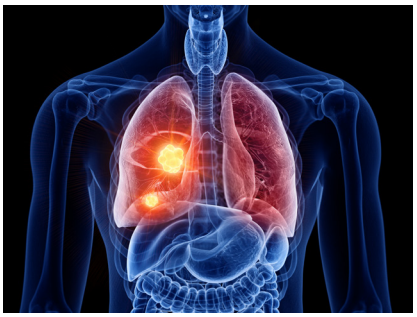
Scientists collaborating in the e:Med Consortium SysINFLAME at the University Hospital Kiel were able to show that biologic therapy with antibodies changes the diversity of microorganisms in the intestines of IBD patients towards the microbiome of healthy people. However, it is not sufficient to draw any conclusions about the therapeutic response of the patient just based on the knowledge of the type of bacteria present in the microbiome. The decisive factors are rather the function of these bacteria and the type of metabolism in the microbiome. In order to better understand the function of the microbiome in IBD patients during treatment with biologic therapy, a systems biology approach was adopted: By stimulating the nutrient exchange of the intestinal bacteria on the computer, it was possible to calculate which metabolic end products were produced. Interestingly, the team of Professor Philip Rosenstiel discovered that patients with appealing biologic therapy had already a completely different metabolism in the microbiome than IBD patients who did not benefit from the therapy.

An exact understanding of which substances are exchanged in the microbiome of the patients can help to identify the defective and disturbing processes in the microbiome of the IBD patients. On this basis, it may be possible in the future to identify exactly which patients can benefit from biologic therapy.

Aden, K., A. Rehman, S. Waschina, W. H. Pan, A. Walker, ... S. Szymczak, ... S. Schreiber, and P. Rosenstiel. (2019) „Metabolic Functions of Gut Microbes Associate with Efficacy of Tumor Necrosis Factor Antagonists in Patients with Inflammatory Bowel Diseases." Gastroenterology

## GENETIC CAUSE OF SMALL CELL LUNG CANCER
## MYC paralog-dependent apoptotic priming

Using a unique cellular CRISPR model, the teams of the e:Med Junior Research Alliance MILES and the e:Med Consortium SMOOSE have discovered a relationship between MYC signaling and the regulation of programmed cell death in small cell lung cancer (SCLC). This finding has a direct impact on the selection of drugs for SCLC patients.



SCLC is the most aggressive subtype of lung cancer with a 5-year survival rate of only 6 %. Chemotherapy is still the standard of care therapy due to the lack of effective targeted therapies for SCLC or predictive markers for patient stratification.

In about 20 % of SCLC patients, genomic amplification of transcription factors of the MYC family occurs. The permanent activation of MYC leads to an upregulation of many genes involved in cell growth and cell survival, ultimately contributing to cancer development. Therefore, MYC represents an ideal target for therapeutic interventions. However, direct therapeutic inhibition of MYC is not yet possible, which means that instead, MYC-activated genes might potentially serve as targets for the development of new inhibitors for the treatment of SCLC.

The scientists, led by Professor Martin Sos (University Hospital Cologne) in collaboration with the Oliver Lab (Huntsman Cancer Institute, Utah), showed that the anti-apoptotic protein BCL2 plays a central role in the sensitivity towards cell cycle inhibitors and inhibitors of the DNA damage repair system in the cells of SCLC patients with activated MYC genes. Apoptosis is a form of regulated cell death that is actively induced within cells with large amounts of genomic damage. Using CRISPR/dCas9-mediated MYC activation, the scientists were able to show that SCLC cell lines with high MYC activity have low BCL2 levels. The resulting lack of BCL2 expression promotes sensitivity towards inhibition of enzymes involved in cell cycle control and the DNA damage repair system. Combined inhibition of proteins, which are involved in cell cycle (Aurora kinase; AURK) or DNA damage repair mechanisms (CHK1) significantly prolonged the survival of mice with MYC-driven SCLC compared to standard chemotherapy. The combination of chemotherapy and the AURK and CHK1 inhibitors also proved to be promising and could prevent the emergence of resistance caused by chemotherapy.

The detailed mapping of MYC-paralog-specific susceptibilities such as low BCL2 levels allowed the identification of molecularly defined drug targets in SCLC patients in order to develop effective therapies and reduce unnecessary side effects through chemotherapy.

Dammert, M. A., ... R. K. Thomas, ... R. Buttner, ... H. C. Reinhardt, ... and M. L. Sos. (2019) „Myc Paralog-Dependent Apoptotic Priming Orchestrates a Spectrum of Vulnerabilities in Small Cell Lung Cancer." Nat Commun.

## CAP OR COPD? BIOMARKER HELPS

## Vesicles deliver biomarkers to discriminate lung diseases

To discriminate fast and precisely between different lung diseases such as community-acquired pneumonia (CAP) and acute exacerbations (AE) of chronic obstructive pulmonary disease (COPD) is important for therapy decision and therefore patient recovery. Appropriate biomarkers could help to accelerate this process and predict disease outcome.

Marburg-based researchers of the e:Med Consortium CAPSyS identified new biomarkers on vesicles to differentiate between lung diseases such as CAP and COPD.

CAP is a major cause of lung disease and death worldwide, especially in children and the elderly. CAP is often inappropriately treated and recognized with delay. It is diagnosed based on symptoms such as cough, fever, pleuritic pain, signs of pulmonary consolidation on auscultation and radiological infiltrates.

COPD is a very common, non-communicable disease characterized by chronic airway inflammation, emphysema and incompletely reversible airway obstructions. Acute exacerbations are phases of acute worsening of COPD symptoms, often in combination with respiratory infection, which need to be treated in hospital due to increased mortality rates.

The e:Med researcher Professor Bernd T. Schmeck (Philipps-University Marburg) and his team identified plasma surface proteins such as the lymphocyte common antigen CD45, the B7 receptor CD28 and the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) from small extracellular vesicles as markers for the diagnosis and differentiation of CAP and AECOPD. Therefore, an extracellular vesicle array with the plasma of healthy donors and patients suffering from COP or AECOPD was performed. The vesicles contain a large number of molecules (nucleic acids, lipids and proteins) and are easily accessible by minimally invasive methods, since the vesicles are found in all body fluids and released by most cell types. Therefore, the vesicles can act as excellent biomarker carrier.

Finding a diagnostic or prognostic biomarker to differentiate between CAP and AECOPD even in the case with COPD-CAP comorbidity and thus predicting the success of therapy in these patients is an important step in personalized medicine to prevent unnecessary use of antibiotics and to apply appropriate treatments to reduce mortality rates and patient expenditure.

Jung, A. L., M. Moller Jorgensen, R. Baek, K. Griss, M. Han, K. Auf Dem Brinke, N. Timmesfeld, W. Bertrams, T. Greulich, R. Koczulla, S. Hippenstiel, N. Suttorp, and B. Schmeck. (2019) „Surface Proteome of Plasma Extracellular Vesicles as Biomarkers for Pneumonia and Acute Exacerbation of Chronic Obstructive Pulmonary Disease.“ J Infect Dis.

## PREDICTING KIDNEY TRANSPLANT SUCCESS

## TreaT urine assay indicates transplant success

Whether a kidney transplant is tolerated by the patient depends on how strongly the recipient's immune system responds to the donor organ cells. Analysis of the recipient's T cells could provide information on the risk of transplant rejection.

So far, however, the T cells that respond to the transplant have not yet been routinely examined and immunosuppressive therapy cannot be individually adapted.

Scientists from the e:Med Consortium e:Kid coordinated by Professor Nina Babel (Charité Berlin) have now developed the TreaT test, which uses cells from the patient's urine after a kidney transplantation to predict how well the recipient will tolerate the donor kidney.

In order to examine the recipient's reactive T cells, ideally the recipient's immune cells must be stimulated with donor kidney cells. So far, this has been the problem: it is difficult to obtain a sufficient amount of donor cells or adequate antigens to stimulate the recipient's T cells in the lab. Therefore, cells from HLA banks have been used for stimulation, but their HLA type

often does not fit optimally. Alternatively, splenocytes are used, but these are only available from deceased donors, in small quantities and do not exactly reflect the tissue specificity.
In contrast, the e:Kid research team uses the urine of already transplanted patients in their TreaT test, which consequently also contains cells from the donor kidney and is both easily accessible and sufficiently available. Renal tubular epithelial cells are extracted from this urine and can be easily collected. The kidney epithelial cells are cultured together with immune cells from the recipient's blood. If a patient has T cells that are specifically directed against the donor cells, these T cells will reactivate and produce specific activation markers and effector cytokines. Using these activation molecules, donor-reactive T cells can be identified, quantified and characterized in more detail. Further investigation has shown that the quantification and characterization of the donor-specific, so-called allogeneic T cells with this *ex vivo* assay is superior to previous tests.

In a small pilot study, this assay was able to identify striking T cell profiles in patients who later suffered from transplant rejection. This newly developed test can employ the reactive T cells to give an indication of how high the risk of rejection is and how well the transplant will be tolerated. On this basis, the accompanying immunosuppressive therapy can thus be adapted to the individual patient and over- or undermedication can be prevented.


Thieme, C. J., B. J. D. Weist, A. Mueskes, T. Roch, U. Stervbo, K. Rosiewicz, P. Wehler, M. Stein, P. Nickel, A. Kurtz, N. Lachmann, M. Choi, M. Schmueck-Henneresse, T. H. Westhoff, P. Reinke, and N. Babel. (2019). „The TreaT-Assay: A Novel Urine-Derived Donor Kidney Cell-Based Assay for Prediction of Kidney Transplantation Outcome". Scientific Reports.

## GENETIC CAUSES OF BIPOLAR DISORDER
## Increased burden of common risk variants for psychiatric disorders

Bipolar disorder (BD) is a mental illness causing periods of depression and abnormally elevated moods. The lifetime risk to develop BD is about one percent in the general population. Nevertheless, according to the WHO, bipolar disorders are among the diseases that lead to the most permanent impairment worldwide. Affected people also have an increased risk of suicide.

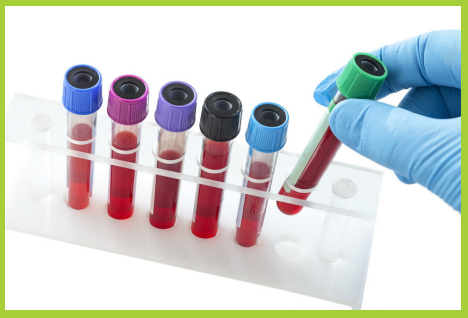
In some families, BD appears in several generations, leading to the overall assumption that individual mutations with high potency of causing BP are responsible for the disease. However, the teams around Professor Marcella Rietschel (ZI Mannheim) as well as around Professor Markus Nöthen (University Hospital Bonn) of the e:Med Consortium Integra-Ment found that frequently occurring genetic risk variants could play a more important role than rare genetic mutations - even in families with many family members suffering from the disease for several generations. Polygenic risk scores for BD and other mental diseases such as schizophrenia were calculated and compared between the different groups (affected family members, unaffected family members and healthy, unrelated people).

Interestingly, the systematic investigation of more than 30 families affected by BD showed that also healthy family members had an increased accumulation of frequently occurring genetic risk variants compared to unrelated healthy people. The accumulation of these risk variants is seen in affected as well as in unaffected family members, whereby the persons suffering from BD showed the highest risk values. Therefore, the researchers suggest a high baseline risk for several psychiatric disorders in these families.
A possible hypothesis could be that these families with a generally increased risk for developing psychiatric disease have a high burden of common variants that confer a specific risk for BD. This contrasts with the earlier assumption that rare gene mutations are the main risk factors for BD.
"Even if it is possible that a cluster of many risk variants with small effects could explain the risk of illness, it cannot be ruled out that more rare variants with greater effects also play a role in these families. We will continue to look for these," says Professor Rietschel.
In the future, an interesting question to be resolved is what factors keep some family members of BD affected families healthy despite the increased appearance of risk variants. This could help to understand the development of BD and improve the life of many people suffering from BD and who are not able to control the changes between phases of depression and mania themselves.

Andlauer, T. F. M., J. Guzman-Parra, F. Streit, ... G. Auburger, F. Degenhardt, S. Heilmann-Heimbach, S. Herms, P. Hoffmann, J. Frank, J. C. Foo, J. Treutlein, S. H. Witt, S. Cichon, M. Kogevinas, F. Rivas, F. Mayoral, B. Müller-Myhsok, A. J. Forstner, M. M. Nöthen, and M. Rietschel. (2019) „Bipolar Multiplex Families Have an Increased Burden of Common Risk Variants for Psychiatric Disorders." J Mol. Psychiatry.

## New Demonstrators for an Individualized Medicine

Increasingly large quantities of medically relevant data can be systematically recorded and analyzed through modern high-throughput procedures and further improvements in bioinformatics.



Thus, the pilot projects **"Demonstrators for an Individualized Medicine"** aim to document the direct benefit and applicability of data records and mathematical modelling in individualized medicine.

Starting in 2019/2020, four new interdisciplinary demonstrator research alliances employ this concept, initially funded by the BMBF with about 8 million EUR:

- **GUIDE-IBD - Molecular therapy control for inflammatory bowel diseases**
(Coordinator: Prof. Dr. Stefan Schreiber, Christian-Albrechts University of Kiel and University Hospital Schleswig-Holstein - Campus Kiel)

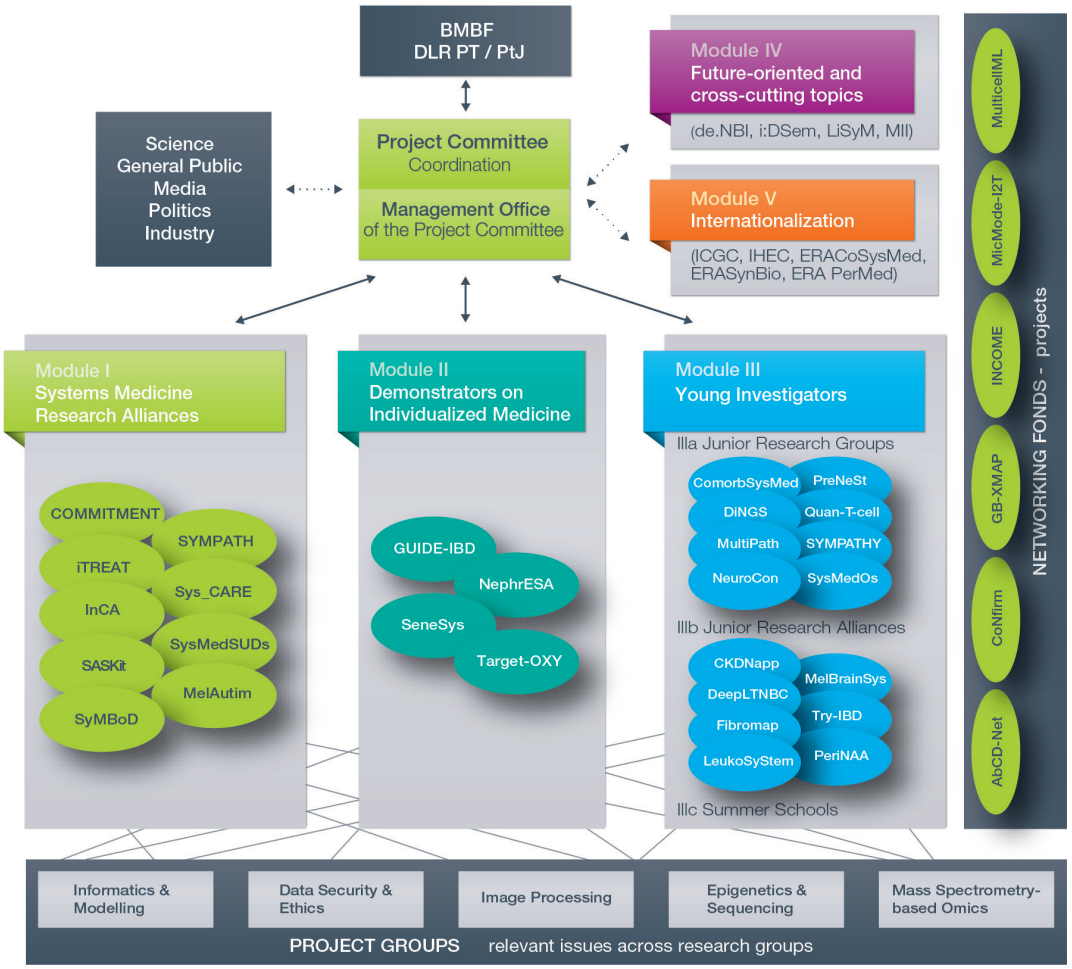
- **NephrESA - A systems biology approach against renal anemia**
(Coordinator: Prof. Dr. Jens Timmer, Albert-Ludwigs-University Freiburg)

- **SeneSys - Senescence-based systems medicine stratification for individualized lymphoma therapy**
(Coordinator: Prof. Dr. med. Clemens Schmitt, Charité Berlin)

- **Target OXY - Towards targeted oxytocin treatment in alcohol addiction**
(Coordinator: Prof. Dr. Rainer Spanagel, The Central Institute of Mental Health - Mannheim)

Focus of the demonstrator projects is on areas of application for which a systems-oriented approach to individualized prevention, diagnosis and therapy of human diseases is required.
Further information:
www.sys-med.de/en/demonstrators

## Structure of e:Med 2nd Generation



# e:Med News

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Here you find information about:

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- networking fonds and project groups
- links to funding info, calendar, events,
- systems medicine news
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