e:Medium NEWSLETTER

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Dear Reader,

We are pleased to introduce the e:Med*ium* - newsletter of the e:Med community. This edition provides you with an overview of the e:Med systems medicine network and gives an understanding of systems medicine-oriented research conducted in its scientific projects. In addition, you will find selected examples showing scientific achievements and the latest highlights of systems medicine in Germany.
Enjoy reading!

The e:Med Management Office

What is e:Med?

The nationwide research program e:Med promotes systems-oriented research into diseases, in order to enable improved prevention, a more comprehensive diagnosis and individually customized therapy models. “e:Med” stands for electronic processing and integration of medically relevant data at various knowledge levels in systems medicine.
In e:Med experts from different specialists areas such as biologists, medical professionals, computer scientists and mathematicians collaborate on cross-disease projects with systems medicine approaches. e:Med is funded by the “Federal Ministry of Education and Research” (BMBF) for an initial period of eight years with up to EUR 200 million and is supported by the project management at German Aerospace Center (DLR) and at Jülich Research Center. The aim of e:Med is the establishment of an active systems medicine network in Germany. The network links hundreds of scientists from 34 clinics and universities, 14 large-scale research centers and six industrial companies in 33 German cities as well as three universities abroad.

CONTENT

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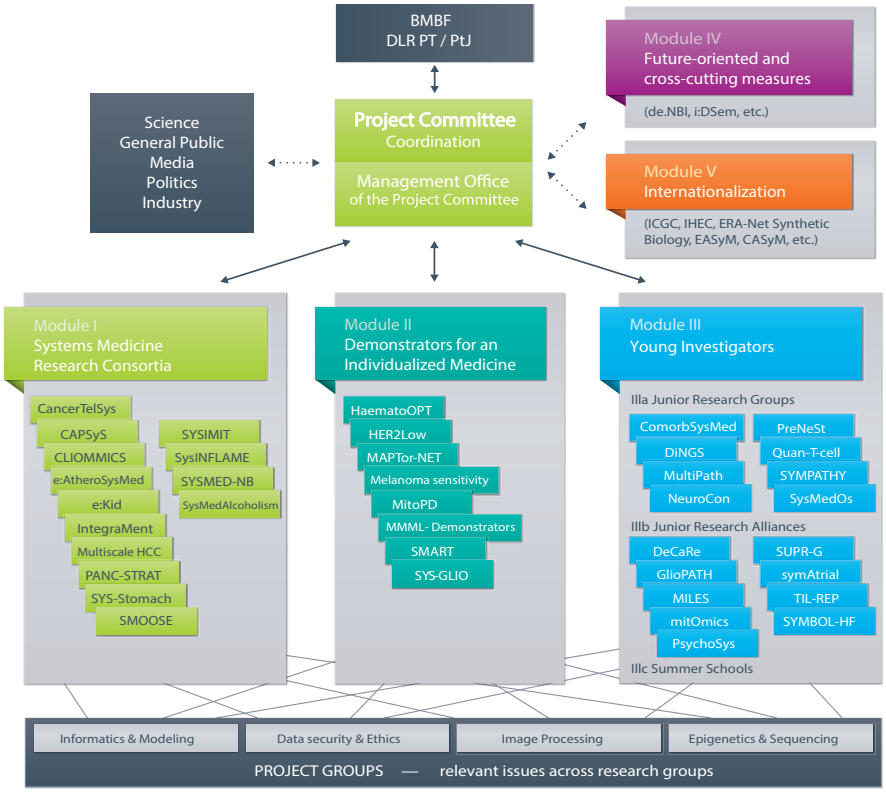
Structure of e:Med

The multifaceted e:Med alliances are grouped into five modules. Members of the project committee are elected from the e:Med community and are the key players in the internal, comprehensive coordination of modules I-III. The e:Med management office acts on behalf of the committee and represents the operational level of coordination. In the e:Med project groups scientists from all modules come together to deal with substantially and methodologically overlapping systems medicine issues. The project management at DLR (DLR PT) and at Jülich Research Center (PtJ) support e:Med on behalf of the BMBF.



Organizational structure of e:Med. The e:Med alliances are listed with their acronym.

Demonstrators

As “Demonstrators for an Individualized Medicine”, eight pilot projects are installed, which should document the direct benefit and applicability of data records and mathematical models that are developed in basic life sciences research for individualized medicine.

The demonstrators are organized as interdisciplinary research groups. The concrete objective is the systems-oriented (further) development of innovative methods and models, which allow for existing data pools to be edited, analyzed and compared with one another. These models and methods are to be used directly in individualized prevention, diagnosis and therapy for human diseases, such as various types of cancer, Parkinson’s disease, heart failure and hematological diseases.

Young Investigators

Junior Research Groups

Eight excellent junior scientists in the area of systems-oriented medical research are pursuing their own long-term research project at a German research institution.

By establishing and managing a research group, young scientists are given the opportunity, to independently and interdisciplinarily build their scientific experience and to establish themselves in the field of systems medicine.

Junior Research Alliances

In nine junior research alliances outstanding young scientists from areas such as biomedicine, clinics and mathematics/information sciences collaborate on questions regarding various types of cancer, neurological diseases or cardiovascular diseases in systems-oriented research approaches.

As a result, knowledge transfer between different fields is intensified and the integration of information science and mathematics in clinical training and research will be enhanced.

e:Med Project Groups

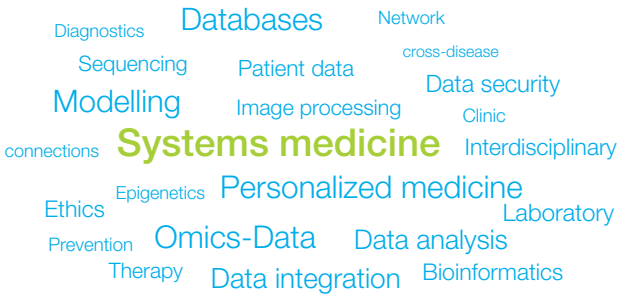
How is it possible to work on research aspects beyond the own specific field? For this purpose, scientists act in four project groups on relevant overarching topics: *informatics & modeling*, *data security & ethics*, *image processing*, and *epigenetics & sequencing*. Here is room for discussion of latest developments and upcoming issues.

The members disseminate important aspects via organizing specific workshops, publications, or surveys. The project groups deal with challenges in systems medicine and promote the exchange of ideas within the e:Med community from which new initiatives result.

Workshops

How handle genomic patient data responsibly, once these are subject of scientific publications by research consortia? To deal with this kind of question, ethicists, scientists and legal experts came together in the workshop „Best Practice - sharing and publishing of human (gen)omics data“. In this discussion session, the focus was on best-practice examples from the consortia. In this context, legal and ethical aspects such as the upcoming European General Data Protection Regulation and the EU-US privacy shield were discussed and questions from the e:Med community were answered. The workshop was organized by the e:Med project group *data security & ethics* in cooperation with the TMF.

Handling of data records from the (bio)informatical perspective was examined in a „Data Management“ workshop. External experts and e:Med members presented and discussed techniques for data integration and data sharing, as well as storage platforms and strategies for combining patient and laboratory data. Based on this workshop a publication about data management is in preparation in order to make it easier for scientists to get started in new systems medicine projects. The workshops were organized by the project group *informatics & modeling*. These Workshops took place at the TMF in Berlin in June 2016.



Consortia

The central measure of the e:Med funding concept consists of the 14 interdisciplinary research consortia. Clinical work groups, biomedical basic research teams employing high-throughput approaches and IT-experts situated at different institutions collaborate closely on the same disease-related issue. The scientists examine systems medicine aspects of different types of cancer, neuropsychiatric diseases as well as cardiovascular and inflammatory diseases.
The objective is to understand the complex molecular networks as a whole, as well as to apply the new findings in developing innovative processes for prevention and diagnostics that are more comprehensive and effective for treatment of diseases in a progressively individualized medicine.

What are the aims of systems medicine?

For Scientists

Experimental design and achievement of sound data (Big Data). Further integration of these data, development of models and confirmation of the data in the lab in iterative cycles towards an optimized outcome.

For Clinicians

Comprehensive, precise and cross-disease information for the individual patient considering the patient data and by integrating the knowledge of complex molecular interactions. Proposal for prevention, therapy option and prognosis for patient treatment.

For Patients

Improved and customized prevention and treatment options taking account of genetic, metabolic, environmental and behavioral influences. Optimized prediction for individual persons considering the enormous knowledge acquired on complex metabolic networks active in one and several diseases.

Scientific achievements

More than 300 research articles are already published in scientific journals and as book chapters or conference articles out of e:Med projects. These include publication in high-impact journals such as Nature, Science and Cell.
The e:Med scientists are engaged in constant dialog. e:Med has so far organized three annual meetings of all members as well as several workshops implying external experts, each event fostering the ongoing projects and creativity for future schemes. In public, e:Med has been present at conferences, in daily newspapers and at trade fairs. Here we cast a glance at three publications.

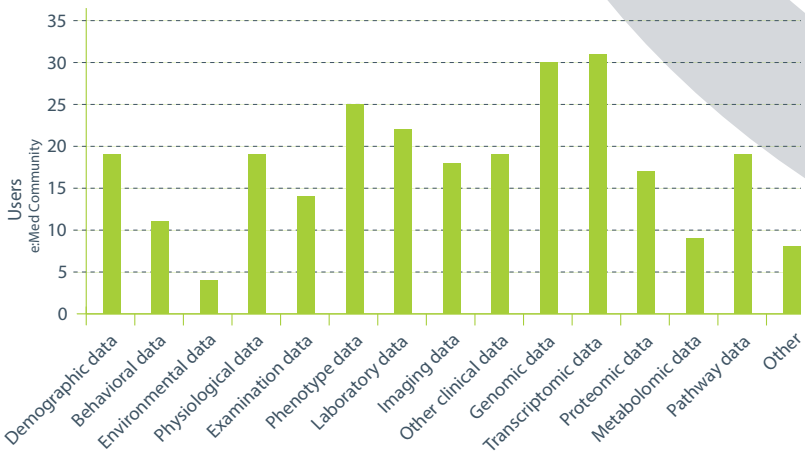
HIGHLIGHT
Finding common ground for various diseases

Cross-disease analysis shows genetic reasons for the common appearance of inflammatory diseases

Many inflammatory diseases surprisingly often appear together. Scientists led by Professor Andre Franke and Professor David Ellinghaus from Kiel, both members of the e:Med Consortium SysINFLAME, now have investigated genetic causes of these chronic inflammatory diseases in a systems medicine approach. Their results show that shared pathophysiological pathways provide the basis for the joint occurrence of the studied diseases. The systems medicine oriented study design – statistical analysis of large genetic cohorts that cover a range of illnesses – allows a better understanding of complex molecular interactions regarding various types of diseases. For their experiments, the scientists chose five frequently jointly appearing diseases affecting the joints, intestine, liver or skin. They examined over 86,000 samples of patients and healthy persons using complex analytical approaches.
Using this method, the researchers discovered 27 new genetic associations, which the diseases examined all have in common. Despite this, the scientists also demonstrated that there are clear genetic differences between the diseases. It is interesting that the genetic signature of patients with several inflammatory diseases is different from patients affected by only one of those. Of the diseases examined an inflammatory liver disease, primary sclerosing cholangitis (PSC) and inflammatory bowel diseases (IBD) very often occur together. The patients show genetic changes that are typical for the PSC-IBD combination and which are different from patients who are exclusively affected by IBD. The authors' overall conclusion is that patients suffering from PSC in combination with IBD in future will have to be classified differently compared to patients only suffering from IBD. The scientists now will include further diseases and clinical data in their studies in order to gain an even more comprehensive overview.
This insight into common features of diseases can help to develop new specialized therapies and to transfer established therapies to other diseases.

Ellinghaus, D., Jostins, L., Spain, S. L., Cortes, A., Bethune, J., Han, B., … Franke, A. (2016). Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. Nature Genetics, 48(5), 510–518. https://doi.org/10.1038/ng.3528

e:Med survey



Systems medicine tools

What expertise and methods do e:Med scientists deploy? Beginning with the project groups informatics & modeling and epigenetics & sequencing, an online survey within the e:Med community showed that there is a broad range of methods and data. Genomic and transcriptomic data in particular is used in many projects and R and Excel are programs frequently used for analysis. The complete evaluation and the contact persons in each case are accessible in the intranet for e:Med members.

Gietzelt, M., Höfer, T., Knaup-Gregori, P., König, R., Löpprich, M., Poos, A., & Ganzinger, M. (2016). The Use of Tools, Modelling Methods, Data Types, and Endpoints in Systems Medicine: A Survey on Projects of the German e:Med-Programme. Studies in Health Technology and Informatics, 228, 670–674. https://doi.org/10.3233/978-1-61499-678-1-670

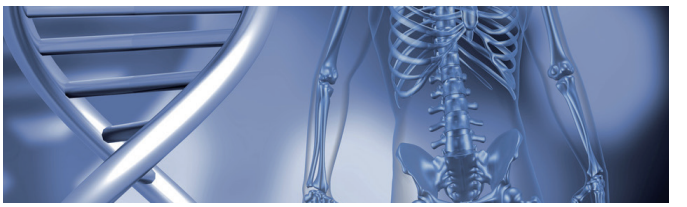
HIGHLIGHT

Mutations take their toll on the bones

Genetic factors are responsible for bone loss with multiple myeloma

Multiple myeloma is a malignant disease of the antibody-producing cells (plasma cells) in bone marrow. In this disease, identical cells multiply excessively in the bone marrow and these produce large quantities of antibodies and pieces thereof. In many patients, this leads to a breakdown of the bones through decreased activity in those cells that are responsible for bone formation and increased activity in the bone-destroying cells. Up to now, it was not known why the bones were attacked in some patients whereas the disease was more moderate in other patients. As the therapy must be selected depending on this aspect of the disease, there is great interest in clarifying the origins of this bone loss. e:Med scientists of the CLIOMMICS consortium around Professor Hartmut Goldschmidt, PD Dr. Dirk Hose and Professor Kari Hemminki from Heidelberg, have identified mutations (SNPs) which genome-wide indicate a strong association with bone loss in multiple myeloma. For this purpose, they examined genomic data of patients with multiple myeloma with the clinical course of the disease and the occurrence of bone loss. The germ line mutations they discovered are in a region of chromosome 8 and chromosome 19. These genetic risk factors are connected with genes that are involved in bone loss and they show that a specific molecular signaling pathway (RANK/RANKL/OPG) is involved. The course of the disease in each case is thus dependent on the individual germ line mutations. The early prediction of the disease course enables a targeted medical intervention and the knowledge of the background to the bone breakdown opens up new therapy options.

Johnson, D. C., Weinhold, N., Mitchell, J., Chen, B., Stephens, O. W., Försti, A., … Morgan, G. J. (2016). Genetic factors influencing the risk of multiple myeloma bone disease. Leukemia, 30(4), 883–888. https://doi.org/10.1038/leu.2015.342



HIGHLIGHT

Cellular rush hour

Tools enabling combined analysis of time-dependent omics data

Along the complex path from gene via transcripts to protein many defects can occur. As a result, individual defects or certain defect combinations can lead to diseases. Extensive information on genetic constitution (genome), gene activity (transcriptome) and resulting proteins (proteome) enable us to gain a better understanding of cellular processes. New high-throughput technologies have made it possible to produce enormous amounts of these genomic, transcriptomic and proteomic data (omics data). Integration and linked analysis of these omics-data, already holds a large amount of information. In addition, if one includes the time factor, these data allow conclusions to be drawn on dynamic processes in cells. Owing to the strong dynamics of cellular processes, temporal resolution offers high information content. However, this analysis represents a bioinformatical challenge. e:Med scientists Astrid Wachter and Professor Tim Beißbarth of the MMML-Demonstrators project have developed a software, based on the statistical platform R, that enables pathway-based integration of time-dependent omics data. Using this application (pwOmics), they have studied the signal paths below the EGF-receptor in more detail. This receptor is important for cell growth and is in many cancer diseases generally overactive. *In silico*-results of e:Med scientists were able to confirm experimental findings and furthermore predicted new interactions. This systems medicine-oriented approach enables us to use large data sets in a broader context and to detect new interactions. This method allows a time-dependent resolution of cellular processes which facilitates a more precise understanding of biological processes.

Wachter, A., & Beißbarth, T. (2015). pwOmics: an R package for pathway-based integration of time-series omics data using public database knowledge. Bioinformatics (Oxford, England), 31(18), 3072–3074. https://doi.org/10.1093/bioinformatics/btv323

Wachter, A., & Beißbarth, T. (2016). Decoding Cellular Dynamics in Epidermal Growth Factor Signaling Using a New Pathway-Based Integration Approach for Proteomics and Transcriptomics Data. Frontiers in Genetics, 6, 351. https://doi.org/10.3389/fgene.2015.00351

e:Med News

PUBLICATIONS

On the e:Med website (**http://www.sys-med.de/en/3/publications**) publications from e:Med projects are listed. Latest publications will be highlighted on the homepage on a newsticker in due course. All e:Med members are asked to inform us about their latest successes so we can make them visible to all.

INTRANET

The e:Med intranet is available to all e:Med and project group members. Here, appointments, addresses and further relevant documents are available. Activities of the e:Med project committee are given and also detailed information on the e:Med project groups. Are you interested? Send us an e-mail to: **info@sys-med.de**

JOB OPPORTUNITIES

Please find open jobs in the various e:Med projects in the "Current" section of our website. If required, we will be glad to place your job opportunities, please contact us at **info@sys-med.de**.

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