



Press Release

Tackling high-risk leukemia: Austrian Science Fund FWF promotes precision oncology at St. Anna CCRI

(Vienna, 20.12.2022) The innovative "ExTrAct AML" project, funded by the Austrian Science Fund FWF, goes beyond established frontiers to investigate acute myeloid leukemia (AML) in children and adolescents. Individual patient profiles should provide early information on the causes of disease progression or treatment resistance – and how to take countermeasures in time. In contrast to previous approaches, these profiles not only include comprehensive (epi)genetic signatures of the leukemia cells, but also their dysfunctional signaling pathways and sensitivity to more than 100 drugs – determined by a new and particularly precise method, that examines the effect of the drugs on cancer cells (pharmacoscopy). The highly endowed FWF grant goes to St. Anna Children's Cancer Research Institute (St. Anna CCRI) and its project partner, the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences.

AML is one of the most serious malignancies in children and adolescents. Despite intensive therapy, this type of leukemia still has a fatal course in about 25% of the patients and the reasons for disease relapses and treatment resistance are so far only partially understood. This is now set to change, thanks to a grant in the amount of € 585,000 from the FWF Clinical Research Program for the project *Linking ex-vivo chemosensitivity, treatment and pathway activations for a deeper understanding of pediatric AML* (ExTrAct-AML).

Scan for key signaling pathways

A team led by Univ.-Prof. Kaan Boztug, MD, Project Leader and Scientific Director of St. Anna CCRI, and Univ.-Prof. Giulio Superti-Furga, PhD, Scientific Director at CeMM, as well as Assoc.-Prof. Michael Dworzak, MD, Principal Investigator at St. Anna CCRI, aims to employ machine learning to create individual risk profiles of patients in order to ultimately provide each child with tailored treatment. Until now, personalized treatment approaches have mostly relied on individual genetic alterations of cancer cells as targets, which actually benefits only a few patients. Kaan Boztug and colleagues hypothesize that, in addition to these known mechanisms, aberrant signaling pathways and metabolic processes of cancer cells are important unexplored mechanisms that could serve as targets. For this reason, – and in contrast to previous projects, which have focused primarily on genetic changes – the researchers in the ExTrAct AML project utilize three independent data sources to create individual risk profiles.

Early identification of patients at risk

First, a team led by Michael Dworzak is applying flow cytometry to create so-called phosphosignal profiles from bone marrow samples. This procedure will reveal the misdirected signaling pathways that lead to the uncontrolled growth of cancer cells.

Second, the researchers are systematically testing 108 already approved drugs and nine selected combination therapies from a drug database created by experts on leukemia cells in the lab. "We use image-based chemosensitivity screening. This method has the great advantage that in the same experiment we see not only the anti-tumor effect of a treatment, but also how it affects the surrounding cells," explains Ben Haladik, PhD student in Kaan Boztug's group.

Third, by using a machine learning based concept, the (epi)genetic landscape of the leukemia cells – characterized by deep disease profiles using next generation sequencing – as well as clinical parameters are also incorporated into individual profiling.



Another new feature of ExTrAct-AML is that the concept focuses on early identification of patients “at risk”, in contrast to most current precision oncology programs, which mostly include patients at a late stage of the disease.

Pioneering pharmacoscopy in pediatrics

"Together with our project partner, CeMM, we are one of few centers in Europe that have first-hand access to the pharmacoscopy technology," highlights Kaan Boztug. Previously, the Superti-Furga lab has demonstrated the efficacy of pharmacoscopy for the treatment of hematological malignancies in adults. Therapies selected by chemosensitivity testing were able to halt disease progression and resulted in significantly better outcomes than the respective prior therapies (*Snijder et al., Lancet Haematol 2017; Kornauth et al., Cancer Discovery 2022*). "With pharmacoscopy, we at CeMM have developed an image-based approach to functional single-cell precision medicine – a technology that enables true personalized medicine in cancer treatment. Now we want to test the potential of pharmacoscopy-guided treatment on a broad scale for the benefit of pediatric patients. This is an important milestone," states Giulio Superti-Furga.

Aim for immediate clinical application

In total, the scientists study bone marrow samples from 45 patients, analyzing at least 50 million cells per patient. In the next step, the team examines the (molecular) signatures obtained in two patient groups of the Italian study group "Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP)-AML" and the German study group "AML-Berlin-Frankfurt-Münster". Further analyses from bone marrow samples of 20 AML patients in Austria and Germany will take place in the prospective AIEOP-BFM 2020 study. Michael Dworzak, vice-chairman of the AML-BFM group, adds: "Thus, the ExTrAct-AML program is embedded in a unique environment of leading clinical experts from national and international AML study centers, which facilitates rapid clinical implementation."

He further notes that this is the first study to combine chemosensitivity and multi-omics data on a specific childhood cancer from a sufficiently large retrospective group as well as a prospective cohort. From the data obtained, the researchers aim to identify patterns of disease progression and treatment resistance. "Despite the genetic diversity of childhood AML, there may be consistent features of disease resistance and progression," explains Kaan Boztug. "We want to provide clinical guidelines for functional *ex vivo* pediatric precision oncology that can be applied to other disease settings."

About pediatric acute myeloid leukemia (PedAML)

PedAML is one of the most serious malignancies in children and adolescents, with about 25% of patients still succumbing to the disease, either due to relapse/resistant disease or to disease and treatment-related complications. Survival is possible only following very intensive chemotherapy in all and additional allogeneic hematopoietic stem cell transplantation in one-third of the patients. A major challenge for the development of targeted therapy approaches in pedAML is the large genetic and molecular heterogeneity, inevitably resulting in small individual cohorts that will be challenging to address in classical clinical trial designs. Notably, pedAML also requires profoundly different therapeutic strategies compared to adult AML with different priorities due to divergence in patient-derived factors and prevalence and frequencies of genetic subtypes. Hence, improvements in the treatment of adults with AML (e.g., FLT3-inhibitors, IDH-inhibitors, and specific protocols for elderly AML patients) can only partially be extrapolated and translated into pediatric disease setting. (*Creutzig U et al. Blood 2012; Bolouri H et al. Nat Med 2018; de Rooij JDE et al., J Clin Med 2015*)



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About the Austrian Science Fund (FWF)

The Austrian Science Fund (FWF) is Austria's leading organisation for funding all fields of basic and arts-based research. Based on a rigorous international peer review process, the FWF supports excellent researchers and their ground-breaking ideas. The insights they gain make Austria a more attractive research location and create the broad knowledge base needed to face the challenges of tomorrow.

About Kaan Boztug

Univ.-Prof. Kaan Boztug, MD, is Scientific Director of St. Anna Children's Cancer Research Institute, Head of Pediatric Immunology at St. Anna Children's Hospital and Professor in the subject field Pediatrics and Inflammation Research at the Medical University of Vienna's Department of Pediatrics and Adolescent Medicine. The internationally renowned expert in rare hematopoietic and immunological diseases is a two-time ERC grant recipient (Starting and Consolidator Grant of the European Research Council) and has received numerous awards honoring his scientific achievements. His work has been published in top journals such as *Blood*, the *New England Journal of Medicine*, and *Nature Genetics*. Kaan Boztug's research group focuses on inborn immune disorders and inherited predisposition to childhood tumors, aiming to understand fundamental mechanisms of immune surveillance relevant to pediatric oncology and immunotherapy approaches.

After his medical studies in Düsseldorf and Freiburg, Germany, and London, followed by a PhD at Scripps Research Institute in La Jolla, USA, Kaan Boztug completed his clinical training and postdoctoral studies at Hannover Medical School. Since 2011, the physician-scientist has been working at the Medical University (MedUni) of Vienna at the Department of Pediatric and Adolescent Medicine and as Principal Investigator at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences. In addition, Kaan Boztug is also Director of the CeRUD Vienna Center for Rare and Undiagnosed Diseases at MedUni Vienna and Director of the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD).

About Giulio Superti-Furga

Univ.-Prof. Giulio Superti-Furga, Ph.D, is CEO and Scientific Director of CeMM, the Research Center for Molecular Medicine of the Austrian Academy of Sciences, and Professor of Medical Systems Biology at the Medical University of Vienna. He was trained as a molecular biologist at the University of Zurich, Genentech, the Research Institute of Molecular Pathology (IMP) Vienna and the European Molecular Biology Laboratory (EMBL) Heidelberg. He co-founded five biotech companies, obtained four ERC grants and has published more than 200 papers. CeMM, that he directs since 2005, is located in the middle of the large general hospital campus in Vienna, where, together with 180 scientists and medical doctors, he is trying to bring the genomic and systems-views close to the clinical world to improve medical practice. For CeMM, he promoted a unique mode of super-cooperation, connecting biology with medicine, experiments with computation, discovery with translation, and science with society and the arts. Recent interests include ways to create functional precision medicine approaches and the role of the human transcriptome in pathophysiology and drug discovery. In addition, Giulio Superti-Furga is the scientific coordinator of "RESOLUTE", a consortium of the "Innovative Medicine Initiative" dedicated to the deorphanization of Solute Carrier (SLC) transporters.

About Michael Dworzak

Assoc.-Prof. Dr. Michael Dworzak obtained his MD from the Medical University of Vienna and joined St. Anna Children's Cancer Research Institute in 1993 as a physician-scientist, combining research and its adaption to clinical work. He is vice chair of St. Anna Children's Hospital in Vienna, section head of Pediatric Oncology & Hematology at St. Anna Children's Hospital, and Associate Professor at the Medical University of Vienna. At Labdia Labordiagnostik GmbH and St. Anna Children's Cancer Research Institute, Michael Dworzak heads the Immunological Diagnostics laboratory, its focus lying on the development of new diagnostic methods for children and adolescents with leukemia and lymphomas



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using flow cytometry immunophenotyping. Michael Dworzak coordinates several international FLOW study groups and networks (iBFM-FLOW, EuPALFLOW). His major achievements include the establishment, clinical validation, and international dissemination of an innovative landmark-technology for response assessment in pediatric leukemias based on flow-cytometric minimal residual disease detection (FLOW-MRD). This eventually led to the integration of FLOW-MRD into clinical treatment protocols, which are applied by an intercontinental consortium for stratification of pediatric patients into relapse risk-based treatment strata worldwide.

Photo

from left: Univ.-Prof. Dr. Giulio Superti-Furga, Univ.-Prof. Dr. Kaan Boztug, Assoc.-Prof. Dr. Michael Dworzak

Credit: Klaus Pichler (1), Harald Eisenberger (2)

About St. Anna Children's Cancer Research Institute, St. Anna CCRI

St. Anna CCRI is an internationally renowned multidisciplinary research institution with the aim to develop and optimize diagnostic, prognostic, and therapeutic strategies for the treatment of children and adolescents with cancer. To achieve this goal, it combines basic research with translational and clinical research and focus on the specific characteristics of childhood tumor diseases in order to provide young patients with the best possible and most innovative therapies. Dedicated research groups in the fields of tumor genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics and clinical research are working together to harmonize scientific findings with the clinical needs of physicians to ultimately improve the wellbeing of our patients.

www.ccri.at www.kinderkrebsforschung.at

About St. Anna Children's Hospital

Since its foundation in 1837, St. Anna Children's Hospital has developed into an institution that offers state-of-the-art medical care in pediatrics and adolescent medicine. In addition to its performance as a general pediatric hospital, St. Anna Children's Hospital has established an excellent reputation throughout Austria as well as internationally as a center for the treatment of hematological disorders and malignancies in children and adolescents. "St. Anna Kinderspital GmbH" is a subsidiary of the Austrian Red Cross (Landesverband Wien), an independent hospital affiliated with the Vienna General Hospital and at the same time the Division of Pediatrics with special focus on Pediatric Hematology-Oncology of the University Hospital for Pediatric and Adolescent Medicine.

www.stanna.at

About CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences

The CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences is an international, independent, and interdisciplinary research institution for molecular medicine under the scientific direction of Giulio Superti-Furga. CeMM is oriented towards medical needs and integrates basic research and clinical expertise to develop innovative diagnostic and therapeutic approaches for precision medicine. Research focuses on cancer, inflammation, metabolic and immune disorders, and rare diseases. The Institute's research building is located on the campus of the Medical University and the Vienna General Hospital. www.cemm.at

About Medical University of Vienna (MedUni Vienna)

MedUni Vienna is one of the most traditional medical education and research facilities in Europe. With almost 8,000 students, it is currently the largest medical training center in the German-speaking countries. With its 6,000 employees 30 university hospitals and two clinical institutes, 13 medical theory



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centers and numerous highly specialized laboratories, it is also one of Europe's leading research institutions in the biomedical sector. MedUni Vienna also has a medical history museum, the Josephinum. Further information: www.meduniwien.ac.at

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