

First worldwide personalized-medicine study using a functional test demonstrates clinical feasibility and efficacy of individualized therapy in leukemia and lymphoma patients; published in *Cancer Discovery*, a journal of the American Association for Cancer Research

Standard therapy for advanced recurring aggressive, hematological malignancies, such as leukemias and lymphomas, have a limited effect with patients experiencing short survival times. A study at the Vienna General Hospital conducted by physicians and scientists from Medical University Vienna and the CeMM Research Center for Molecular Medicine (CeMM), as well as ETH Zurich for the first time demonstrated that therapy selection based on results from a functional test is clinically possible and effective in patients with recurrent hematologic cancers. The researchers quantified drug effects on single cells from real-time patient biopsies using a novel experimental technique, resulting in 56 patients receiving individually tailored treatment – with significant positive outcome. The work is published in *Cancer Discovery* (Impact Factor: 39.4), a Journal of the American Association for Cancer Research.

(Vienna, October 12, 2021) The central aim of personalized medicine is to find the right treatment for the right patient at the right time by analyzing and using specific characteristics of the patient's tumor. Until now, personalized therapy-matching has been primarily done based on genetic biomarkers. However, these provide treatment options for less than 10% of cancer patients. On the other hand, functional precision medicine (FPM) utilizes functionally evaluates the efficacy of numerous drugs directly on cancer cells, similar to the testing of antibiotics in an antibiogram.

This study tested a novel approach of FPM, specifically termed "single-cell functional precision medicine (scFPM)", where the response to drugs on healthy and malignant cells, isolated from freshly removed tissue from cancer patients, is investigated with an in-depth analysis. Consequently, the method facilitates identification of drugs that show cancer cell specific efficacy, while plausibly exhibiting a reduction in side effects. High precision of this platform is achieved with automated high-content microscopy and computerized image analysis, formerly called "pharmacoscopy".

Within the framework of the EXALT (Extended Analysis for Leukemia/Lymphoma Treatment) study, focusing on patients with advanced hematological cancers, physicians and scientists led by Philipp Staber (MedUni Vienna/University Hospital Vienna), Ingrid Simonitsch-Klupp (MedUni Vienna/University Hospital Vienna), Giulio Superti-Furga (CeMM), and Berend Snijder (ETH Zurich, formerly CeMM) were for the first time able to show that therapy guidance by a functional test is clinically feasible and beneficial for cancer patients. The first authorship of the publication is shared by Christoph Kornauth and Tea Pemovska (both MedUni Vienna/University Hospital Vienna), as well as Gregory Vladimer (Exscientia, formerly CeMM).

Testing drug efficacy

"We examined patients' tumor cells of real-time biopsies and directly tested the effects of more than 130 candidate compounds to determine which therapy would be effective in each patient," said Principal Investigator of the study, Philipp Staber, Associate Professor at the Clinical Department of Hematology and Hemostaseology at MedUni Vienna and the Vienna General Hospital and a member of the Comprehensive Cancer Center (CCC). "To test the individual benefit of patients, the response time to therapy was compared with that to their respective prior therapy. 54% of our patients had a significant, at least more than 30% prolonged time of progression-free survival under the scFPM-guided therapy. 21% of all patients even showed a long-term response. Our study demonstrates that individual therapy tailoring is feasible, and effective in breaking resistance to prior therapies," says Staber. The image-based scFPM approach was developed in the research group of CeMM Principal Investigator and Scientific Director Giulio Superti-Furga, also Professor of Molecular Systems Biology at the MedUni Vienna. Giulio Superti-Furga adds: "We wanted to enable true personalized medicine in cancer treatment. For years, many, like us at CeMM and MedUni Vienna, have been working on ever-improving molecular profiles of genes, proteins and metabolites that should facilitate individualized treatment of patients. But the approach used here is a kind of a shortcut. We're directly testing which drug actually works on the cancer cells. The idea of personalized cancer medicine is far from new. But many years of research have gone into developing technology behind analyzing tumor tissue in such a way that therapy-relevant information can be extracted. Today, we can perform single-cell analyses of patient samples with unprecedented resolution and precision, observe individual immune cell interactions, and thus test the effect of an enormous variety of drugs."

Targeted therapy selection

This is the first systematic prospective evaluation of a precision medicine cancer approach using a direct functional assay to instruct n-of-one therapies. Thus, active substances were directly tested on the patient's cell material in order to derive an individually tailored anti-cancer therapy. The most advanced patients with aggressive hematological cancers clearly benefited from the approach and the findings validate the utility, efficacy, and feasibility of integrating functional drug testing in clinical routine.

Picture attached: Philipp Staber, Christoph Kornauth, Tea Pemovska and Giulio Superti-Furga ©CeMM

The study "Functional Precision Medicine Provides Clinical Benefit in Advanced Aggressive Hematological Cancers and Identifies Exceptional Responders" was published in the journal *Cancer Discovery* on Oct. 11 2021. DOI: 10.1158/2159-8290.CD-21-0538

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Philipp Staber is an Associate Professor at the MedUni Vienna, head of the Functional Precision Hematology research group and director of the clinical programs for lymphoma, chronic lymphocytic leukemia and T-cell lymphoma at the MedUni Vienna and the AKH.

Ingrid Simonitsch-Klupp is an Associate Professor at the Clinical Institute of Pathology at MedUni Vienna, head of the "Hematopathology" working group.

Berend Snijder is an assistant professor at the Institute of Molecular Systems Biology at the ETH Zurich, and group leader at the Swiss Institute for Bioinformatics. His research group, funded by the European Research Council and the Swiss National Science Foundation among others, aims to understand why patients can respond so differently to their treatment, using systems biology approaches that integrate deep learning-enhanced Pharmacoscopy with molecular patient profiling.

Giulio Superti-Furga is the Scientific Director of CeMM and Professor of Medical Systems Biology at the Medical University of Vienna. His current research areas of interest include ways to create functional approaches in precision medicine and the role of human membrane transporters in pathophysiology and drug discovery. Fostering young talent through new collaborative and inclusive approaches, uniting basic research and its medical translation, and technological innovation for the benefit of patients and society are of particular interest to him.

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

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The **Vienna Healthcare Group's University Hospital Vienna** treats around 80,000 inpatients every year. In addition, approximately 1.2 million people visit its outpatient clinics and specialized outpatient clinics. Together with the doctors from MedUni Vienna, there are a total of 3,000 nurses to look after our patients, more than 1,000 members of the medical, therapeutic and diagnostic healthcare professions and additional staff from many different professional groups.

The **Comprehensive Cancer Centre** (CCC) Vienna belonging to MedUni Vienna and University Hospital Vienna provides a network for all professionals from these two institutions who treat cancer patients, conduct cancer research and are active in teaching and education in this field. (www.ccc.ac.at)

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