CML: A new combination therapy against resistant leukemia

(Vienna, 6.2.2024) In a new publication in the *American Journal of Hematology*, scientists at St. Anna Children's Cancer Research Institute show a treatment option for chronic myeloid leukemia with highly resistant multiple mutations that have eluded previous therapies.

Chronic myeloid leukemia (CML) is a slowly progressing cancer. It affects 1.5 people per 100,000 inhabitants, children and adolescents can also be among the patients. Thanks to a therapy based on tyrosine kinase inhibitors (TKIs), the 10-year survival rate of patients has improved drastically, namely to 80-90 per cent, so that life expectancy is not limited if there is a good response to treatment.

The TKIs inhibit a protein, the BCR::ABL1 fusion protein, which plays a central role in the development of leukemia. However, even this treatment is not always successful if the leukemic cells develop resistance. Genetic changes to individual nucleic bases of the DNA in the BCR::ABL1 fusion gene, so-called point mutations, are often the problem. New generations of TKIs can usually overcome resistance caused by such point mutations, but if the leukemia cells develop more than one point mutation, even the latest drugs can be ineffective. For highly resistant double mutations, so-called compound mutations, there has been no effective drug therapy option with single available TKIs, so far.

New option against highly resistant compound mutations

This is where Thomas Lion, MD, PhD, MSc, Principal Investigator at St. Anna Children's Cancer Research Institute and Medical Director of Labdia Labordiagnostik GmbH, and his team came in. In a study on CML leukemia cell models, which was recently published in the *American Journal of Hematology*, he and his colleagues investigated combination therapies with ponatinib, the strongest drug to date, but toxic in higher doses. The team was able to show that the combination of low-dose ponatinib with other, also low-dose drugs, in particular with the recently approved drug asciminib, was very effective in the model system studied, although the substances individually showed no effect even at high doses. This means that effective treatment options for CML with highly resistant compound mutations are now available for the first time and initial observations in patients indicate that the in vitro test results could also be used successfully in the clinical situation. Study author Lion says: "Thanks to the low doses of the drugs in the successfully tested combination therapies, we can hope that we will also have not only effective but also less toxic treatment options available for CML patients with highly resistant compound mutations. This will bring us closer to our goal of being able to offer effective treatment options for all CML patients."

About St. Anna Children's Cancer Research

The St. Anna Children's Cancer Research Institute (CCRI) is an international and interdisciplinary research institution that aims to further develop and improve diagnostic, prognostic and therapeutic strategies for the treatment of children and adolescents with cancer through innovative research. Taking into account the specific characteristics of childhood tumor diseases, dedicated research groups in the fields of tumor genomics and epigenomics, immunology, molecular biology and cell biology work together to reconcile the latest scientific and experimental findings with the clinical needs of doctors and to sustainably improve the well-being of young patients.
www.ccri.at; www.kinderkrebsforschung.at;

About Labdia Labordiagnostik GesmbH
Ambulatorium Labdia Labordiagnostik GmbH was founded in 2006 as a non-profit subsidiary of the St. Anna Children's Cancer Research Institute (CCRI) with the aim of developing and offering new diagnostic procedures. Its activities focus on the fields of hematology/oncology, immunology, infectiology and human genetics.
www.labdia.at

About Thomas Lion
Thomas Lion, MD, PhD, MSc, studied medicine and social sciences in Vienna and biology/genetics in Chicago and Prague. He is a professor at the Medical University of Vienna and head of the Department of Molecular Microbiology at St. Anna Children's Cancer Research Institute. As a specialist in pediatrics and adolescent medicine with a focus on haemato-oncology as well as medical and chemical laboratory diagnostics, he is the medical director and managing director of Labdia Labordiagnostik GesmbH.

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