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CHILDREN'S CANCER RESEARCH INSTITUTE

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Press Release

Gene Mutation in the Immune System: Anti-Diabetes Drugs Make Immune Cells More Effective Again

(Vienna, 31.08.2023) **T cells are an essential component of the immune system - they fight foreign structures such as bacteria and viruses or cancer-related changes in cells. This defense reaction requires energy. Scientists led by the St. Anna Children's Cancer Research Institute and the Marmara University Istanbul have now shown for the first time that a defect in the gene for the transcription factor NFATC1 leads to an immune defect with a disruption of metabolism in T lymphocytes. They were also able to show in a cell culture model that this metabolic disturbance of the immune cells was improved by the administration of established anti-diabetic drugs. The study has now been published in the prestigious journal *Blood*.**

Immune metabolism is a central topic of research. Which nutrients are absorbed and how they are processed is determined not only by the cell, but also by its function. T cells must be able to process glucose (sugar) to do their vital job, the response to pathogens or cancer cells. If this metabolism is disturbed, the performance of this function will be insufficient. Scientists under the lead of the St. Anna Children's Cancer Research Institute (St. Anna CCRI) and the Marmara University Istanbul have now been able to show for the first time that a mutation of the transcription factor NFATC1, which is important for the activation of T cells, causes a previously unknown inborn immune defect: The affected patients suffer from recurrent infections and inflammations.

The first author of the study, which has now been published in the journal *Blood*, Sevgi Köstel Bal, MD, PhD, a postdoctoral researcher at the St. Anna CCRI in the group of Kaan Boztug, MD, speaks of a rare disease, but one that can be a model for immune metabolism and deliberate intervention in it. It has been seen very clearly, she says, that a T cell needs energy. However, if glucose cannot be processed, the human body becomes ill. One can picture this in terms of a car that doesn't run optimally because the fuel can't be processed properly. By administering an anti-diabetic drug that has been known for decades, such as metformin or rosiglitazone, “the immune cells increasingly resorted to fats as an energy source," says Sevgi Köstel Bal. “So in a way we trained the immune cells."

Training the cells on fat

The drugs are usually administered in type 2 diabetes to facilitate the uptake of insulin to convert carbohydrates into energy. "We believe there is huge potential in the field of immune metabolism for improving immune cell function for some defects by targeting immune metabolism. In our study, we were not only able to discover a new immune defect, but more importantly, we were able to show that the function of the patient’s immune cells could be improved by normalizing the metabolism in the immune cells, even though it is an inborn immune defect.," said Kaan Boztug, last author of the study, Scientific Director at the St. Anna CCRI, Professor at the Medical University of Vienna and Adjunct Principal Investigator at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences (ÖAW).

Whether the *NFATC1* mutation, like many other inborn immune system gene defects, increases the risk of cancer in humans remains to be definitively determined, Boztug says. The question of whether the defect can cause an autoimmune reaction, i.e. the destruction of the body's own cells by the human body, has also not yet been answered. In the mouse model, this reaction has indeed already been demonstrated. Research is therefore still needed to understand the NFATC1 gene defect and its effects in further detail. This is also the view of Safa Baris of the Marmara University, co-last author of the study, Professor of Pediatric Allergy and Immunology. He led the clinical care of the patients and was critically involved in the scientific collaboration between Istanbul and Vienna.

In the future the results of the *Blood*-study could indeed lead to personalized therapies that target the molecular causes of immune diseases specifically - with the help of immunomodulation. Deliberately influencing the immune system with drugs to fine-tune without causing an overreaction or suppression would be a significant advance in the treatment of rare diseases like this, Boztug says.

Publication

Biallelic NFATC1 mutations cause an inborn error of immunity with impaired CD8+ T-cell function and perturbed glycolysis
Köstel Bal S, Giuliani S, Block J, Repiscak P, Hafemeister C, Shahin T, Nurhan K, Ransmayr B, Miao Y, Van de Wetering C, Frohne A, Jimenez Heredia R, Schuster M, Zoghi S, Hertlein V, Thian M, Bykov A, Babayeva R, Bilgic Eltan S, Karakoc-Aydiner E, Shaw LE, Chowdhury I, Varjosalo M, Argüello RJ, Farlik M, Ozen A, Serfling E, Loïc Dupré L, Bock C, Halbritter F, Hannich JT, Castanon I, Kraakman MJ, Baris S#, Boztug K#
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About Kaan Boztug

Kaan Boztug, MD, is the Scientific Director of the St. Anna Children's Cancer Research Institute, Senior Physician in Pediatric Hematology and Oncology, Head of the Immunology Department at the St. Anna Children's Hospital, and Professor in the Department of Pediatrics and Adolescent Medicine at the Medical University of Vienna. He is an internationally recognized expert in rare diseases of blood formation and the immune system, and a two-time recipient of the ERC Grant (ERC Starting and Consolidator Grant). He has been honored with numerous awards for his scientific work. Under his leadership, scientific papers have been published in top journals such as the *New England Journal of Medicine*, *Blood*, *Nature Immunology*, and *Nature Genetics*. Kaan Boztug's research group focuses on inherited bone marrow failure syndromes, immune deficiencies, and inherited predisposition to childhood tumors. Their aim is to understand fundamental mechanisms of immune surveillance that are relevant to pediatric oncology and immunotherapy approaches.

After studying medicine in Düsseldorf, Freiburg, and London, and completing his doctoral studies at the Scripps Research Institute in La Jolla, USA, Kaan Boztug underwent clinical training and postdoctoral research at the Hannover Medical School. Since 2011, he has been working as a physician and researcher at the Medical University of Vienna in the Department of Pediatrics and Adolescent Medicine, as well as an Adjunct Principal Investigator at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences. In addition, Kaan Boztug is also the Director of the CeRUD Vienna Center for Rare and Undiagnosed Diseases at the Medical University of Vienna and has been the Director of the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases.

About the St. Anna Children's Cancer Research Institute
The St. Anna Children's Cancer Research Institute (CCRI) is an international and interdisciplinary research institution dedicated to advancing diagnostic, prognostic, and therapeutic strategies for the treatment of children and adolescents with cancer through innovative research. Incorporating the specific characteristics of childhood tumor diseases, dedicated research groups collaborate in the fields of tumor genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics, and clinical research. Their aim is to bridge the latest scientific and experimental knowledge with the clinical needs of physicians in order to significantly improve the well-being of young patients. For more information, visit www.ccri.at or www.kinderkrebsforschung.at.

About the Medical University of Vienna
The Medical University of Vienna (MedUni Vienna) is one of the most prestigious institutions for medical education and research in Europe. With approximately 8,000 students, it is the largest medical training institution in the German-speaking region. With 6,000 employees, 30 university clinics, two clinical institutes, 13 medical-theoretical centers, and numerous highly specialized laboratories, it is considered one of the most significant biomedical research institutions in Europe. The MedUni Vienna also houses the Josephinum, a museum of medical history. For more information, visit www.meduniwien.ac.at.

About the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences (ÖAW)
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 leadership of Giulio Superti-Furga. CeMM is guided by medical needs and integrates basic research with clinical expertise to develop innovative diagnostic and therapeutic approaches for precision medicine. The research focuses on cancer, inflammation, metabolic and immune disorders, rare diseases, and cellular aging processes. The research facility is located on the campus of the Medical University of Vienna and the General Hospital Vienna. For more information, visit www.cemm.at

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