



St. Anna Kinderkrebsforschung
CHILDREN'S CANCER RESEARCH INSTITUTE



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Press Release

Cancer in children with rare inborn immune defect: High cure rate if treated early

New research data highlight a marked predisposition to lymphoma, a type of cancer, in children harboring specific gene mutations. A significant fraction of these rare mutations also cause inborn immune defects associated with recurrent infections. Under the leadership of Kaan Boztug, LBI-RUD and CCRI Director and CeMM Adjunct Principal Investigator, and collaborating closely with leading centers across the world, researchers investigated patients bearing recently identified defects in two molecules termed CD27 and CD70. In contrast to previously reported high mortality rates associated with lymphoma in a part of this population, the present results are encouraging: a high cure rate was achieved if patients received stem cell transplantation soon after diagnosis. Published in the *Journal Blood*, the study gives insights into clinical course and early immunological parameters as well as treatment response in the largest group of children with CD27 or CD70 deficiency to date.

A worldwide study may contribute to cure children with specific inborn mutations, by providing unprecedented insights into disease characteristics. The underlying mutations, namely in the genes encoding CD27 and CD70, cause inborn errors of the immune system (immunodeficiencies). A major threat to these immuno-compromised patients are infections, primarily with Epstein-Barr virus (EBV). The impaired immune system cannot cope with this infection, and the virus persists in the blood. Subsequently it causes severe disease, including lymphoma. This is a type of cancer originating from infection-fighting cells of the immune system, termed lymphocytes.

Given the rarity of these mutations, no consensus on how to treat affected children exists. Previous observations had shown that patients with CD27 or CD70 deficiencies have a significantly increased risk of death during the first occurrence of lymphoma. To improve outcome, the recently published study for the first time reports in-depth clinical and immunological characterization of the largest patient cohort (n=49) with CD27 or CD70 deficiency reported to date.

Remarkable results in a rare disease

The new data highlight the marked predisposition to lymphoma of both CD27 and CD70 deficient patients. For children with severe Epstein-Barr virus associated disease, or lymphoma, genetic investigation of CD27 and CD70 is essential. This could optimize clinical management and most importantly support in making a timely decision for curative hematopoietic stem cell transplantation.

“In our study population we report excellent outcome following hematopoietic stem cell transplantation in patients with severe disease manifestations, predominantly lymphoma”, study senior author Assoc.-Prof. Kaan Boztug, MD, comments. 18 out of 19 (95%) patients who received stem cell transplantation just after their first malignant event could be cured. This means they are cancer free after a median follow-up of two years. Co-first author Sevgi Köstel Bal, MD, PhD, adds, “Our results provide a strong rationale for timely use of this curative treatment in patients with CD27 or CD70 deficiencies upon lymphoma diagnosis.”

Consider immune defect in children with cancer

Designed as a retrospective analysis, the study included clinical information of 49 patients from 20 centers all over the world. 33 patients presented with CD27 and 16 with CD70 deficiency.

The majority (90%) of patients had an Epstein-Barr virus infection at diagnosis of CD27 or CD70 deficiency. 36% of CD27 deficient patients and 56% of CD70-deficient patients developed lymphoma at a median age of 8.5 or three years, respectively. Another frequent event was autoinflammation, which appeared in various forms in 21 patients (43%). Autoinflammation is an aberrant inflammatory reaction affecting the body's own tissues that derives from the innate immune system.



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Major findings relate to immunological characteristics, mechanisms of disease pathogenesis and clinical course of individual patients undergoing various treatments. These findings highlight the critical role of CD27-CD70 interaction in regulating immunity, especially in the context of Epstein-Barr virus control and formation of lymphoma. The new data underline that an immune defect should be considered as underlying cause when children present with cancer, in particular if there is a history of recurrent infections or inability to control Epstein-Barr virus.

Largest cohort due to world-wide approach

Performed in close collaboration with the Inborn Errors Working Party of the European Society for Immunodeficiencies (ESID) and the European Society for Bone and Marrow Transplantation (EBMT), this study reports the to date world's largest cohort of patients with mutations in either CD27 or CD70. This was only possible in a multicenter effort, led by the study centers in Vienna, Sydney, Düsseldorf, Leiden, Tehran, and Ankara.

Publication:

Extended Clinical and Immunological Phenotype and Transplant Outcome in CD27 and CD70 Deficiency.

S Ghosh*, S Köstel Bal*, E S J Edwards*, B Pillay, R Jimenez-Heredia, G Rao, F Erol Cipe, E Salzer, S Zoghi, H Abolhassani, T Momen, E Gostick, D A Price, Y Zhang, A J Oler, C Gonzaga-Jauregui, B Erman, A Metin, I Ilhan, S Haskologlu, C Islamoglu, K Baskin, S Ceylaner, E Yilmaz, E Unal, M Karakukcu, D Berghuis, T Cole, A Kumar Gupta, F Hauck, A Hoepelman, S Baris, E Karakoc-Aydiner, A Ozen, L Kager, D Holzinger, M Paulussen, R Krüger, R Meisel, P Thomas Oommen, E C Morris, B Neven, A J J Worth, J M van Montfrans, P Fraaij, S Choo, F Dogu, E G Davies, S Burns, G Dueckers, R Perez Becker, H von Bernuth, S Latour, M Faraci, M Gattorno, H Su, Q Pan-Hammarström, L Hammarström, M J Lenardo, C S Ma, T Niehues, A Aghamohammadi, N Rezaei**, A Ikinciogullari**, S G Tangye**, A C Lankester**, K Boztug**

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Figure

(Credit: Tatjana Hirschmugl, Blood. 2020; <https://doi.org/10.1182/blood.2020006738>. doi:10.1182/blood.2020006738)

Title: **The study at a glance**

Abbreviations:

AB=antibiotic

alloHSCT=allogeneic hematopoietic stem cell transplantation

def=deficiency

EBV=Epstein-Barr virus

HLH=hemophagocytic lymphohistiocytosis

IgG=Immunoglobulin G

Picture

(Credit: St. Anna Children's Cancer Research Institute)

Sevgi Köstel Bal, MD, PhD and Assoc.-Prof. Kaan Boztug, MD

About St. Anna Children's Cancer Research Institute (CCRI)



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The 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, we combine 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

About Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD)

LBI-RUD was founded in April 2016 in a joint effort of Ludwig Boltzmann Society, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Medical University of Vienna, and St. Anna Children's Cancer Research Institute. The three founding partner institution, and CeRUD Vienna Center for Rare and Undiagnosed Diseases, constitute LBI-RUD's most important collaboration partners.

Research at LBI-RUD focuses on the deciphering of rare immunological, hematopoietic, nervous, dermal, gastro-intestinal, and hepatic diseases. Those studies provide unique insights into human biology, and are the basis for the development of tailored therapeutic concepts in the sense of the personalized medicine of the future.

The mission of LBI-RUD is – together with its partner institutions – to sustainably develop and maintain research infrastructure integrating scientific, societal, ethical, and economical aspects of rare diseases.

www.rare-diseases.at

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

The mission of CeMM is to achieve maximum scientific innovation in molecular medicine to improve healthcare. At CeMM, an international and creative team of scientists and medical doctors pursues free-minded basic life science research in a large and vibrant hospital environment of outstanding medical tradition and practice. CeMM's research is based on post-genomic technologies and focuses on societally important diseases, such as immune disorders and infections, cancer and metabolic disorders. CeMM operates in a unique mode of super-cooperation, connecting biology with medicine, experiments with computation, discovery with translation, and science with society and the arts. The goal of CeMM is to pioneer the science that nurtures the precise, personalized, predictive and preventive medicine of the future. CeMM trains a modern blend of biomedical scientists and is located at the campus of the General Hospital and the Medical University of Vienna.

www.cemm.oeaw.ac.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 26 university hospitals and two clinical institutes, 12 medical theory centers and numerous highly specialized laboratories, it is also one of Europe's leading research establishments in the biomedical sector.

www.meduniwien.ac.at

Further Information

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