Newly discovered, rare immunodeficiency yields unexpected insights into the immune system

---Scientists in Austria are world leaders in rare and undiagnosed diseases research---

A hitherto unknown gene mutation revealed the role of a key molecule for immune cell development. An international team of scientists led by Kaan Boztug from CeMM Research Institute for Molecular Medicine of the Austrian Academy of Sciences, the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases and the Medical University at Vienna gained fundamentally new insights into the human immune system by studying this newly discovered mutation. Moreover, their research revealed a potential personalized therapy for this rare disease. The study, published in *Nature Immunology*, clearly highlights the importance and opportunities of research in the field of rare diseases.

(Vienna, 24th of October, 2016) A twelve-year old patient was the starting point of the study: Since his birth, the child suffered from severe, life-threatening infections. Immunological analyses showed a disturbed ratio of white blood cells, the so-called lymphocytes, hampering his immune system to fight efficiently against invading pathogens. Three of his six siblings died within the first two years of life, presumably due to similar complications. Although the origin of their condition was unknown, the researchers assumed a genetic trait in four severely diseased children of the same family.

To investigate rare patients like these, the new Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD) was founded in Vienna. In collaboration with CeMM, the Medical University Vienna and the St. Anna Children's Cancer Research Institute, LBI-RUD was established by the Ludwig Boltzmann Gesellschaft in April 2016. “The accumulated expertise of our institute is unique” states Kaan Boztug, Director of the LBI-RUD and head of the study. “We are the ideal place to find the molecular cause of rare – and most often genetic – diseases, and to develop this knowledge into targeted therapies”.

“Our analyses of the patient’s and his parents’ genomes indeed confirmed that the boy’s disorder had a genetic cause”, explains Elisabeth Salzer, postdoctoral fellow at CeMM and first author of the study. Using next generation sequencing – a modern and highly efficient genetic method to detect disease-causing mutations – the researchers found an error in the gene encoding RASGRP1, a key protein for the development of lymphocytes. The healthy parents, as well as the three healthy siblings, only had one copy of the mutation in their genome, while the diseased boy had inherited both faulty copies from his parents.

Until this time, the function of RASGPR1 in the immune system was only partially studied in rodent models. Its role in humans was unknown, and a mutation that inhibited the protein had never been reported. The case of the 12-year old patient not only showed that the lack of RASGRP1 impairs T lymphocytes, but also that the protein plays a so far unknown role for maintaining the cellular scaffold (cytoskeleton) in natural killer (NK-) cells. Through a series of further experiments, the researchers were able to analyze the faulty molecular circuits in greater detail.

Eventually, the scientist even found an approved drug, lenalidomide, that has the potential to reverse some effects of the newly discovered RASGRP1 deficiency. Therefore, this study is a prime example for

the importance and opportunities of studying rare diseases – as it is done at the LBI-RUD: "The whole process from the discovery of a gene defect as cause for a rare disease to the exploration of the disease-causing mechanism to the development of a personalized therapy does much more than helping the affected patients", explains Kaan Boztug, "Virtually every case – such as the immunodeficiency of this young patient – provides profound new insights into the human organism and paves the way towards a future precision medicine."

Attached pictures: 1.: Kaan Boztug and Elisabeth Salzer, senior and first author of the study (©CeMM/Wolfgang Däuble). 2.: Artwork showing RASGRP1-dependent vesicle transport towards the immunological synapse (© LBI-RUD/Tatjana Hirschmugl).

The Study "RASGRP1 deficiency causes immunodeficiency with impaired cytoskeletal dynamics responsive to lenalidomide", *Nature Immunology*, doi**: 10.1038/ni.3575**

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Funding: This study was supported by the European Research Council (ERC), the Vienna Science and Technology Fund (WWTF), Celgene Austria, the National Institutes of Health (NIH), fellowships from the Boehringer Ingelheim Fonds and the Austrian Research Fund (FWF) Lise Meitner Programme.

Kaan Boztug studied Medicine in Düsseldorf, Freiburg and London, followed by his graduate training with Iain Campbell at the Scripps Research Institute (La Jolla, USA), and clinical training and postgraduate research with Christoph Klein at Hannover Medical School (Germany). He joined CeMM in 2011 and holds a dual appointment as Associate Professor at the Department of Paediatrics and Adolescent Medicine at the Medical University of Vienna. Since 2016, Kaan Boztug is director of the Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases. He is also director of the recently established CeRUD Vienna Center for Rare and Undiagnosed Diseases and joint director of the Jeffrey Modell Foundation Center for Immunodeficiencies at the Medical University of Vienna and St. Anna Children's Hospital.

CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences is an interdisciplinary research institute committed to advancing the understanding of human diseases through basic and biomedical research. Located at the center of the Medical University of Vienna's campus, CeMM fosters a highly collaborative and interactive research mindset. Focusing on medically relevant questions, CeMM researchers concentrate on human biology and diseases like cancer and inflammation/immune disorders. In support of scientific pursuits and medical needs, CeMM provides access to cutting-edge technologies and has established a strategic interest in personalized medicine. Since 2005, Giulio Superti-Furga is the Scientific Director of CeMM. http://www.cemm.oeaw.ac.at/

The **Ludwig-Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD)** was founded by the Ludwig Boltzmann Gesellschaft GMBH in April 2016, in collaboration with CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, the Medical University Vienna and the St. Anna Children's Cancer Research Institute. The research at LBI-RUD focuses on the elucidation of rare

diseases of the hematopoiesis, the immune system and the nervous system. Those efforts may provide the basis for the development of personalizes therapies for the directly affected patients, and can also offer unique and novel insights into human biology. Taking advantage of the expertise of its partner organizations, the goal of the LBI-RUD is to establish a coordinated research program that advances the scientific, social, ethical and economic implications of rare diseases.

The **Medical University at Vienna** is a medical training and research institutions of Europe which has some of the richest traditions. It is today the largest medical training institute in the German-speaking area with over 8,000 students. With its 27 university hospitals, three clinical institutes, 12 theoretical medicine centres and numerous highly specialised laboratories, it is included among the most important cutting-edge research institutes of Europe in the area of biomedicine. Its own laboratory building with highly specialised "Core Facilities" was inaugurated in June 2010 with the "Anna Spiegel Research Building".

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