***Inherited DOCK2 deficiency in patients with early-onset invasive bacterial and viral infections***

**(Vienna, 17 June 2015) In an international study scientists from Kaan Boztug´s team at CeMM and the Medical University of Vienna, in close collaboration with the groups of Luigi Notarangelo at Boston Children’s Hospital, and Jean-Laurent Casanova at Rockefeller University, New York, have elucidated the molecular cause of a hitherto unrecognized inherited disorder of the immune system (primary immunodeficiency). Performing genetic and cellular immunological studies, the researchers identified biallelic mutations in *DOCK2*, a gene encoding a protein of critical importance for the cytoskeleton. Patients affected by this rare disease exhibit broad defects of immunity, including defective cellular motility and effector function of various types of leukocytes. The findings have been published online, on 18th June, 2015, in the New England Journal of Medicine.**

According to the EU-wide definition, a disease is classified as rare if it occurs in no more than five people per 10,000 inhabitants. Often, far fewer people suffer a rare disease, of which there are estimated to be up to 8,000 different ones. To foster better diagnostics, research, and clinical care of patients with rare diseases, the Medical University of Vienna together with CeMM have recently established the Vienna Center for Rare and Undiagnosed Diseases (CeRUD) in Vienna. Although a number of primary immunodeficiencies have been identified, a large number remains elusive. Accordingly, a scientific focus at CeRUD lies in the investigation of undefined immunodeficiency disorders, conducted by Kaan Boztug, whose research group has identified several novel types of immunodeficiency disorders since his relocation to Vienna in 2011. Recognition of such disorders has a huge impact beyond the individual patient, as it allows for a molecular understanding of the hierarchical composition of the human immune system and its core components as well as their involvement in molecular networks. From the molecular characterization of these diseases, patients may profit through more specific diagnostics and the development of targeted therapeutic approaches in the future.

In their publication, CeMM PhD student Cecilia Domínguez Conde along with shared first authors Kerry Dobbs, Sheng-Ying Zhang and Silvia Parolini used a next generation sequencing-based approach to identify autosomal recessive mutations in *DOCK2* in five unrelated families. The patients were characterized by a history of life-threatening bacterial and viral infections during infancy and early childhood. DOCK2 is an activator of the signaling molecule Rac1 which regulates cytoskeletal rearrangements and signaling events. Adequate control of the cytoskeleton is particularly important for immune cells, since they critically depend on regulated actin dynamics to enable migration and immune cell signaling. The defects resulting from *DOCK2* mutations included impaired chemokine-induced migration in B and T cells and cytotoxic activity of NK cells. In addition, the authors identify an unexpected role for DOCK2 in non-hematopoietic cells including deficient antiviral immunity, which may explain the marked susceptibility to viral infections in these patients. Due to the severity of the disease, the authors find that allogeneic hematopoietic stem cell transplantation should be performed early after detection, and may be efficient in providing long-term immune reconstitution.

**CeMM Research Centre for Molecular Medicine of the Austrian Academy of Sciences (CeMM) – brief profile**

CeMM is an international, independent and interdisciplinary research institute for molecular medicine. “From the clinic for the clinic” – CeMM is guided by medical needs, and integrates fundamental research with clinical expertise in order to develop innovative diagnostic and therapeutic approaches. Its research projects focus on cancer as well as on inflammatory and immunological disorders. For further information, please visit www.cemm.oeaw.ac.at.

**Medical University of Vienna (MedUni Wien) – brief profile**

The Medical University of Vienna is one of the longest-established medical training and research institutions in Europe. With almost 7,500 students, it is today the largest medical training body in the German-speaking world. With its 31 university hospitals, 12 medical research centres and many highly specialised laboratories, it is also among the most important cutting-edge biomedical research centres in Europe. It offers over 48,000 m² of clinical research space.

**Publication**

Inherited DOCK2 Deficiency in Patients with Early-Onset Invasive Infections. Kerry Dobbs, B.S., Cecilia Domínguez Conde, M.Sc., Shen-Ying Zhang, M.D., Ph.D., Silvia Parolini, Ph.D., Magali Audry, Ph.D., Janet Chou, M.D., Emma Haapaniemi, M.D., Sevgi Keles, M.D., Ivan Bilic, Ph.D., Satoshi Okada, M.D., Ph.D., Michel J. Massaad, Ph.D., Samuli Rounioja, M.D., Ph.D., Adel M. Alwahadneh, M.D., Nina K. Serwas, M.Sc., Kelly Capuder, B.S., Ergin Çiftçi, M.D., Kerstin Felgentreff, M.D., Toshiro K. Ohsumi, Ph.D., Vincent Pedergnana, Ph.D., Bertrand Boisson, Ph.D., Şule Haskoloğlu, M.D., Arzu Ensari, M.D., Ph.D., Michael Schuster, Ph.D., Alessandro Moretta, M.D., Yuval Itan, Ph.D., Ornella Patrizi, Ph.D., Flore Rozenberg, M.D., Pierre Lebon, M.D., Janna Saarela, M.D., Ph.D., Mikael Knip, M.D., Ph.D., Slavé Petrovski, Ph.D., David B. Goldstein, Ph.D., Roberta E. Parrott, B.S., Berna Savas, M.D., Ph.D., Axel Schambach, M.D., Ph.D., Giovanna Tabellini, Ph.D., Christoph Bock, Ph.D., Talal A. Chatila, M.D., Anne Marie Comeau, Ph.D., Raif S. Geha, M.D., Laurent Abel, M.D., Ph.D., Rebecca H. Buckley, M.D., Aydan İkincioğulları, M.D., Waleed Al-Herz, M.D., Merja Helminen, M.D., Ph.D., Figen Doğu, M.D., Jean-Laurent Casanova, M.D., Ph.D., Kaan Boztuğ, M.D., and Luigi D. Notarangelo, M.D. *New England Journal of Medicine* DOI: 10.1056/NEJMoa1413462 (2015).

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