

## A New Achilles' Heel of Blood Cancer

**Acute Myeloid Leukemia (AML) is an aggressive form of blood cancer that frequently develops in children. The diseased cells often carry mutated forms of a specific gene, which is known to function within large protein networks. Applying a combination of high-throughput proteomic and genomic screens in AML cells, researchers at CeMM and LBI-CR identified a protein of this network crucial for the survival of the cancer cells. When this protein is lost, AML cells stop growing and accumulate DNA damage, which makes them more sensitive to anti-cancer drugs – a novel potential approach for targeted therapies. The study was published in *Nature Communications*.**

(Vienna, May 18, 2018) AML is not a single disease. It is a group of leukemias that develop in the bone marrow from progenitors of specialized blood cells, the so-called myeloid cells. Rapidly growing and dividing, these aberrant cells crowd the bone marrow and bloodstream, which can be fatal within weeks or months if the disease is left untreated. Myeloid cells of various types and stages can become cancerous and cause AML, which makes the condition very heterogeneous and difficult to treat. Thus, finding drug targets that affect as many forms of AML as possible is a prime goal for researchers.

Mutations in the MLL (Mixed lineage leukemia) gene are of interest, as they are frequent in AML. They are caused by rearrangements of big chunks of DNA, so-called chromosomal translocations, which can lead to the fusion of two otherwise-separated genes; in the case of the MLL gene, fusions with more than 75 different partner genes were found. Above that, it was known that MLL-fusion proteins act in the context of large protein complexes, which need specific “effector” proteins to exert their oncogenic function – ideal targets for a precise therapy. However, it was not clear whether such critical effectors are common for all MLL-fusion proteins.

The research groups of Florian Grebien from the Ludwig Boltzmann Institute for Cancer Research, Giulio Superti-Furga, Scientific Director of the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, and Johannes Zuber, from the Institute of Molecular Pathology, tackled that question in their latest study. They were able to identify common, conserved molecular mechanisms that drive oncogenesis in the context of the large number of different MLL-fusion proteins by characterizing the protein-protein interaction networks of distantly related MLL fusion proteins. Their results were now published in *Nature Communications* (DOI: 10.1038/s41467-018-04329-y)

The scientists, with CeMM PhD-Student Anna Skucha as first author of the study, characterized the entire protein complexes around seven different MLL fusion proteins in detail, which revealed

128 conserved interaction partners of MLL fusions. In further functional experiments, that were carried out in collaboration with the IMP Vienna and the Medical University Vienna, they identified the methyltransferase SETD2 as a critical effector of MLL-fusion proteins. Using genomic techniques including CRISPR/Cas9 genome editing, the researchers found that SETD2 loss caused induction of DNA-damage and ultimately cell death in the cancer cells. Moreover, SETD2 loss increased the lethal effect of Pinometostat, a drug that is currently in clinical development for treatment of leukemia patients with MLL fusions. These experiments might pave the way for a more effective therapy in the future using a combination of compounds.

“These data highlight the relevance of combined proteomic-genomic cellular screening to identify critical effectors of genes involved in the development of acute myeloid leukemia” Florian Grebien, one of the senior authors of the study, explains. “Our results establish a novel role for SETD2 in the maintenance of genomic integrity during initiation and progression of MLL-rearranged AML and contribute to further clarification of the molecular mechanisms driving MLL-fusion-dependent leukemogenesis”

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**The study** “MLL-fusion-driven leukemia requires SETD2 to safeguard genomic integrity” was published in *Nature Communications* on May 18, 2018. DOI: 10.1038/s41467-018-04329-y

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**Florian Grebien** did his PhD jointly supervised by Ernst Müllner of the Medical University Vienna and Hartmut Beug of the Research Institute for Molecular Pathology (IMP) in Vienna. For his post-doctoral research he joined the team of Giulio Superti-Furga at the Research Center for Molecular Medicine (CeMM) of the Austrian Academy of Sciences, Vienna. Since 2014 he leads an independent research team at the Ludwig Boltzmann Institute for Cancer Research (LBI-CR). In January 2018, he was appointed Professor and head of the institute for Medical Biochemistry at the University of Veterinary Medicine Vienna. Florian Grebien's research is funded by the starting grant "ONCOMECHAML" from the European Research Council (ERC).

Florian Grebien's research focuses on acute myeloid leukemia (AML), a cancer of white blood cells that is characterized by the rapid growth of abnormal myeloid cells that accumulate in the bone marrow and interfere with the production of normal blood cells. The laboratory of Florian Grebien aims to contribute to a better understanding of the molecular mechanisms of leukemia development through the development and use of novel tools for functional evaluation of oncogenic aberrations.

The mission of **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** 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.

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