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New strategy to target transcription factor STAT5 to combat leukaemia

Acute myeloid leukaemia (AML) is the most common type of acute cancer of the blood and bone marrow in adults. This type of cancer usually progresses quickly and only 26 percent of the patients survive longer than 5 years as resistance against established treatments arises. The most common molecular cause is FLT3 mutations, which result in hyper-activation of STAT5. An international consortium of researchers now report on an early preclinical development to target STAT5 directly, which cooperates well with existing therapies.

The term „hematopoietic cancer“ refers to several, in most cases quite severe health conditions in which the process of blood cell production is altered. Cancers of white blood cells are characterized by enhanced proliferation and reduced differentiation and cell death in one myeloid lineage, which can promote the outgrowth of a dominant myeloid cell type. The transformation to AML is the most devastating complication experienced by patients. This type of cancer usually progresses quickly and despite considerable advances in therapeutic approaches and allogeneic hematopoietic stem cell transplantation, only 26% of patients survive longer than 5 years. These conditions are frequently caused by mutations that over-activate intracellular signalling or gene transcription. Activating mutations in the receptor FLT3 represent 30% of driver mutations in AML, which in turn activates STAT5, an important transcription factor for blood cell transformation. Targeting the mutated proteins with small molecular weight drugs is currently the leading strategy for combating cancer. However, while FLT3 inhibitors induce responses in AML-patients with FLT3 mutations initially, responses are not durable, and AML progresses in virtually all patients. New treatment strategies are therefore urgently needed to improve patient survival of this aggressive disease.

Transcription factors like STAT5 are similar to genetic light switches and capable of turning genes on and off. But previous strategies to target STAT transcription factors have been difficult and failed on potency or a lack of specificity. An international consortium of researchers from Austria, Canada and Hungary now report on a novel compound which targets STAT5 directly and selectively. Researchers led by Richard Moriggl, director of the Ludwig Boltzmann Institute for Cancer Research and Professor for Functional Cancer Genomics in a joint appointment to the University of Veterinary Medicine, Vienna and Medical University Vienna chose to target the SH2 domain of STAT5, which is essential for the interactions between STAT5 proteins and their subsequent activity.

The researchers aimed at development, synthesis and preclinical testing of a new compound that targets the oncogenic functions of STAT5 proteins. Upon state-of-the-art computational molecular modelling the compound was synthesised and tested in a broad array of tests. In the study now reported in the prestigious Nature Group journal *Leukemia*, the compound not only binds directly to STAT5, it subsequently also disrupts STAT5 activation, nuclear translocation, and STAT5-dependent gene transcription. Bettina Wingelhofer, first author of the publication, used the compound in several leukemic cells, “we could show that our novel compound might be a good drug candidate as it impaired the proliferation of patient derived AML cell lines at low concentrations.” Importantly the compound showed efficacy in freshly isolated patient samples in experiments carried out with the team of Peter Valent (Medical University Vienna), speaker of SFB-F47 and international clinical expert for AML. Initial experiments in combinations with established drugs showed that the new compound cooperatively inhibited tumour cell proliferation. Further research in cooperation with a pharmaceutical company will be required to validate this new compound class with further improvements to validate if it is indeed suitable to be used in a clinical trial.

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Bettina Wingelhofer, Barbara Maurer, Elizabeth C. Heyes, Abbarna C. Cumaraswamy, Angelika Berger-Becvar, Elvin D. de Araujo, Anna Orlova, Patricia Freund, Frank Ruge, Jisung Park, Gary Tin, Siawash Ahmar, Charles-Hugues Lardeau, Irina Sadovnik, Dávid Bajusz, György Miklós Keserű, Florian Grebien, Stefan Kubicek, Peter Valent, Patrick T. Gunning and Richard Moriggl, Pharmacologic inhibition of STAT5 in acute myeloid leukemia, *Leukemia* (2018), doi:10.1038/s41375-017-0005-9

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About the Ludwig Boltzmann Institute for Cancer Research (LBI-CR):

The LBI-CR focuses on developing new murine models for cancer and exploiting them to gain novel insights into the origins of the disease. The institute conducts cutting edge research into the underlying mechanisms of cancer using the modern power of genetics. With particular attention for signal cooperation in tumour cells the researchers analyse the molecular basis of cancer with the intention to translate recent progress in cancer research into novel therapeutic approaches. The Institute conducts its research in close cooperation with the Research Institute for Molecular Pathology, Medical University Vienna, Veterinary University, Children's Cancer Research Institute and the company Tissuegnostics.

About the Ludwig Boltzmann Gesellschaft:

The Ludwig Boltzmann Gesellschaft (LBG) is a research institution with a thematic focus on medicine, life sciences and the humanities, and is specifically targeting new research topics in Austria. Together with academic and implementing partners, the LBG is currently running 19 institutes and develops and tests new forms of collaboration between science and non-scientific actors such as companies, the public sector and civil society. Socially relevant challenges, to which research can contribute, are to be recognized at an early stage and taken up. The LBG Open Innovation in Science Center, which unlocks the potential of open innovation for science, and the LBG Career Center, which supports 200 pre- and postdocs, as well as two new research groups on mental health are part of the LBG. The LBG employs 550 people.