IMP Press Release

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Research Institute of Molecular Pathology

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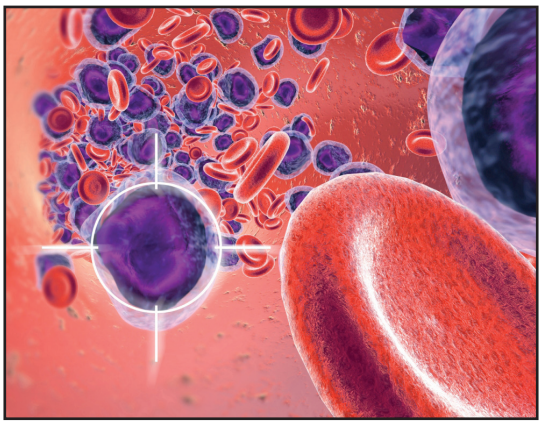
Arrow in the Achilles heel of leukemia – potential new active ingredient yields promising results

A new potential active ingredient against acute myeloid leukemia has been indentified and successfully tested by scientists in the USA. Johannes Zuber, now group leader at the IMP in Vienna, was in charge of the study.

Acute myeloid leukemia (AML) is an aggressive form of leukemia that is uncontrollable in 70% of patients. But a potential new therapy is in sight, one that was discovered in a way that is highly unusual for tumor research. Scientists were looking not so much for the cause of leukemia as for a genetic "Achilles heel": a chink in this cancer's armor. They found the Brd4 gene. Promising results have already been achieved with a previously developed inhibitor against this protein. This successful discovery was made by scientists from the Cold Spring Harbor Laboratory in New York, predominantly Johannes Zuber and his former colleague Junwei Shi. Zuber has now established his own research group at the Research Institute for Molecular Pathology (IMP) in Vienna.
"The new potential active ingredient is not only proving to be extremely effective against leukemia cells; tests so far indicate only minimal damage to healthy, non-defective cells," said Christopher Vakoc, team leader in Cold Spring Harbor, about two essential requirements the active ingredient must meet before it is considered a candidate.
Johannes Zuber explained the innovative approach the researchers selected: "Cancer is clearly a genetically-determined disease. But it is not necessary to examine each mutation in detail. We were more interested in identifying the genes a tumor depends on to stay alive. For example, we know that the chromatin parts regulating how DNA is read are significantly altered in leukemia and other cancer cells." This group of chromatin-modified genes was therefore systematically tested as a potential starting point for therapy.

Systematic weak-spot analysis in acute myeloid leukemia

The research was carried out on an especially virulent form of acute-myeloid leukemia that is mostly immune to chemotherapy and cannot be cured. For the systematic analysis of 243 known chromatin-regulators, the scientists used "hairpin technology", a technology Zuber had optimized for studies into tumor models as a post-doctoral researcher in scientist Scott Lowe's laboratory in Cold Spring Harbor. Here small RNA molecules that resemble hairpins were used to destroy the larger molecules of messenger RNA (mRNA). mRNA is responsible for transferring information from genotype (DNA) to ribosome (protein factories). If they are destroyed, the gene affected cannot be transformed into protein and is thus "switched off".
When a gene that is clearly essential for the survival of the tumor is switched off, significant improvements in disease patterns follow. This success was particularly dramatic in one gene: Brd4. The suppression of the gene led to an immediate halt of division and even to the death of leukemia cells, significantly slowed the progression of the disease, and thus extended the life of a mouse with leukemia significantly.
"With Brd4 we have found the Achilles heel of this form of leukemia", exclaimed Zuber. Brd4 regulates myc, which as an oncogene plays a role in the development of 50% of all types of cancer and evidently keeps leukemia cells alive.



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A new active agent against acute myeloid leukemia

Development work on a therapy for this malignant form of leukemia can now move forward more rapidly than previously thought. Coincidentally, JQ1, an inhibitor precisely for this pivotal Brd4 gene, has recently been developed by James Bradner at the Dana-Farber Cancer Institute in Boston. Comprehensive tests show that JQ1 completely blocks the chromatin binding of Brd4, and is thus lethal for leukemia and possibly other types of cancer as well. Although the majority of these analyses took place in Cold Spring Harbor, significant contributions were also made in Vienna. In addition to setting up his own laboratory at the Research Institute for Molecular Pathology (IMP), Johannes Zuber has also established a promising cooperation with Peter Valent's research group at the AKH (Vienna General Hospital). This cooperation has already led to the first successful tests of the new active agent on patient leukemia cells in Vienna. Johannes Zuber hopes that "clinical studies can begin soon".

Original publication:

Zuber, J. et. al. 2011. RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukemia. Nature.

Illustration, Download & Legend:

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With the help of "hairpin technology" the leukemia cell's weak spot, the Brd4 gene, was targeted and switched off. A significant improvement in the disease pattern followed.

Johannes Zuber:

Johannes Zuber was born in Dresden in 1974. He finished his medical studies at the Humboldt University in Berlin in 2003 with a PhD in molecular cancer research. As a medical assistant at the Charité University Clinic, he focused his clinical and scientific work on hematopoietic-system tumors. In 2005 he moved the USA, where he researched innovative potential therapies for leukemia at Prof. Scott Lowe's laboratory in Cold Spring Harbor. Since January 2011 Johannes Zuber has been a group leader at the Research Institute for Molecular Pathology in Vienna.

IMP:

The Research Institute for Molecular Pathology carries out foundational biomedical research in Vienna. Its main sponsor is Boehringer Ingelheim, an international corporate group. At IMP more that 200 researchers from over 30 countries work on solving basic molecular and cellular processes in order to understand the details of complex biological phenomena. Areas of research include cellular and molecular biology, neurobiology, pathogenesis and bioinformatics. IMP is a founding member of the Campus Vienna Biocenter.

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