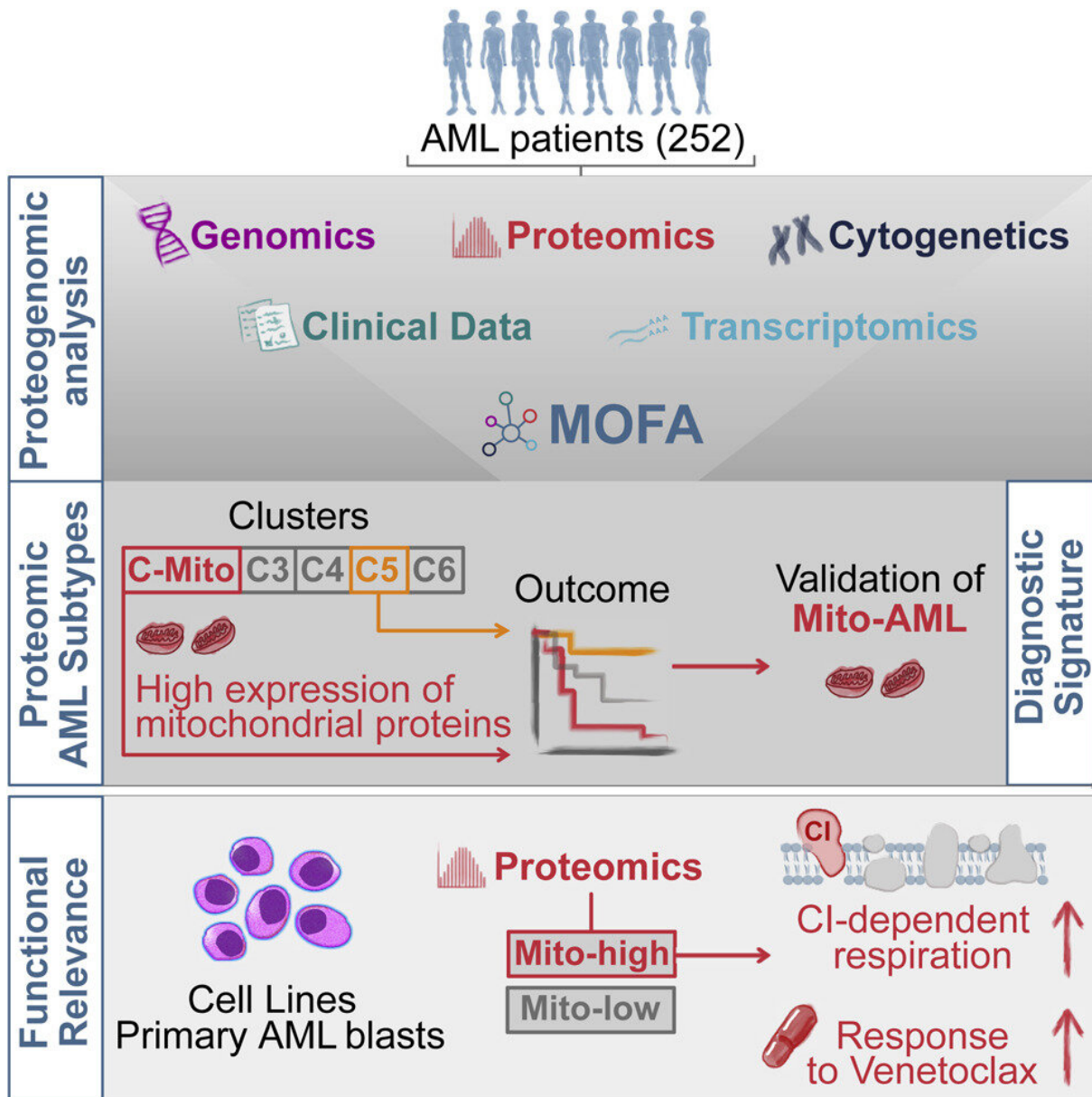


# Proteogenomics identifies novel acute myeloid leukemia subtypes

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In order to better treat patients diagnosed with acute myeloid leukemia (AML), the pathological processes and also existing subtypes of the disease must be better understood. With the help of proteome and genome analysis, researchers at the Max Planck Institute (MPI) of Biochemistry in Martinsried, together with cooperation partners from the University Hospital in Frankfurt am Main, have discovered a new subtype. This subgroup contains elevated levels of mitochondrial proteins and thus has altered mitochondrial metabolism. These so-called mito-AML cells can be combated more effectively in laboratory experiments with the help of inhibitors against mitochondrial respiration than with conventional chemotherapeutic agents. The study was published in *Cancer Cell*.

## Identification of molecular AML subtypes

Acute myeloid leukemia (AML) is an aggressive cancer originating from blood cells. When immature blood cells in the [bone marrow](#) acquire certain aberrations in their genome they become malignant and overgrow the bone marrow, the place where normally blood cells are produced. As a consequence, normal [blood cells](#) are suppressed by the leukemia cells and this leads to infections, bleeding and ultimately death of patients. Most patients diagnosed with AML undergo chemotherapy.

In the last decades [genomic studies](#) identified molecular subtypes of the disease thereby opening up a perspective for personalized [therapeutic approaches](#) in AML. As a result, Clinicians and researchers now distinguish different genomic AML subtypes and for some of them they now even use specific therapeutics. These discoveries have certainly revolutionized the molecular understanding of the disease. However,

despite this progress, prognosis for AML remains poor, highlighting the strong medical need for a deeper understanding of AML pathophysiology and for further innovative and more efficient therapies.

## **Proteomic and genomic data from mass spectrometry**

In an [interdisciplinary approach](#), scientists around Matthias Mann (MPI of Biochemistry), Thomas Oellerich and Hubert Serve (both University Hospital Frankfurt, DKTK & DKFZ) investigated whether the proteome of AML cells could aid in the identification of disease subtypes, biomarkers and therapeutic approaches. To study the protein expression profiles in AML, the team used mass spectrometry, a technology that allows to identify and quantify proteins by detecting their specific weight. In parallel, they characterized the genome of AML cells by DNA and RNA sequencing technologies.

By combining the proteomic and genomic data, several proteogenomic AML subtypes were identified, each representing specific biological features. Importantly, one subtype was only evident at the proteome level and hence was not discovered before. This subtype was characterized by high expression of mitochondrial proteins, a rewired mitochondrial metabolism and clinical resistance to chemotherapy, and was for this reason named Mito-AML. Since mitochondria are the power houses within [cells](#), the research team further investigated whether the disease-specific metabolic alterations in Mito-AML can be therapeutically exploited. In a series of experiments, they found that drugs that interfered with mitochondrial respiration such as the BCL2 inhibitor venetoclax are highly effective in Mito-AML cell culture, and thus might be a more effective therapy compared to traditional chemotherapeutics. Subsequently, it can now be tested whether the laboratory results are also confirmable in clinical patient studies.

## **New treatment approaches for AML through interdisciplinary cooperation**

The first authors of the study, Ashok Kumar Jayavelu, (formerly MPI of Biochemistry and now group leader at the German Cancer Research Center, DKFZ, Heidelberg), Sebastian Wolf (University Hospital Frankfurt) and Florian Buettner (University Hospital Frankfurt, DKTK & DKFZ) agree: "AML is a very aggressive disease and is one of the most common blood cancers in adults. By combining our expertise from clinical, basic and data science we were able to discover disease pathophysiology, the Mito-AML subtype, that will likely influence our understanding of AML and also future clinical developments."

Hubert Serve says: "This finding became possible by close collaboration between clinicians from Frankfurt University and the Study Alliance Leukemia (SAL), a nationwide network dedicated to improve the treatment of AML, and basic scientists. It will help us to better understand why some patients respond better than others to different forms of therapy."

Matthias Mann and Thomas Oellerich further add: "The discovery of the Mito-AML subtype demonstrates the strong potential of mass spectrometry-based proteomics technology for the identification of clinically relevant biomarkers and drug targets. Our study clearly shows that genomic and proteomic data are complementing each other, thereby enabling us to elucidate so far undescribed aspects of disease biology and to nominate innovative treatment approaches. Our approach led to the discovery of new molecular AML subtypes with clinical relevance and thereby provides a proteomic nosology as a basis for an improved molecular understanding and clinical classification of AML."

**More information:** Ashok Kumar Jayavelu et al, The proteogenomic

subtypes of acute myeloid leukemia, *Cancer Cell* (2022). [DOI: 10.1016/j.ccell.2022.02.006](https://doi.org/10.1016/j.ccell.2022.02.006)

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