Acute myeloid leukemia (AML) is a subtype of leukemia that has extremely poor prognosis. AML affects both children and adults with an incidence of approximately 12,000 new patients in the U.S. each year. Current treatment methods include chemotherapy, radiation and stem cell transplant. Although considerable progress has been made in understanding the causes of AML, the drugs currently used to treat these diseases are little changed over the past 40 years and yield disappointing results. The overall five-year survival rate of AML patients is less than 20%. More effective treatments are needed.

Research in recent years shows that mutations of histone methyltransferases including mixed lineage leukemia (MLL), MLL3, enhancer of zest (EZH2) and nuclear receptor binding and SET domain containing protein 1 (NSD1) are enriched in AML [1,2], suggesting epigenetic mechanism is involved in initiation and development of leukemia. They also highlight the potential of targeting epigenetic pathways as an area for development of novel therapeutics.

Indeed, several lead compounds targeting proteins (i.e. MENIN, DOT1L and BRD4) in the MLL pathway have shown therapeutic potential in the treatment of AML that carry MLL gene rearrangement [3-5]. These compounds target recruitment of MLL fusion proteins [3] or MLL fusion protein associated transcription cofactors [4,5]. As a result, they changed leukemia cell transcriptome, which is essential for proliferation and survival of cancer cells. One advantage of these compounds is that they all target leukemia blasts, which often escape conventional therapy.

The demonstrated efficacy by targeting epigenetic pathway breaks new ground for the treatment of AML patients. Future studies with these leads will likely reveal novel mechanisms for subtypes of AML as well as the potential for developing combination therapies for this class of aggressive diseases.

References