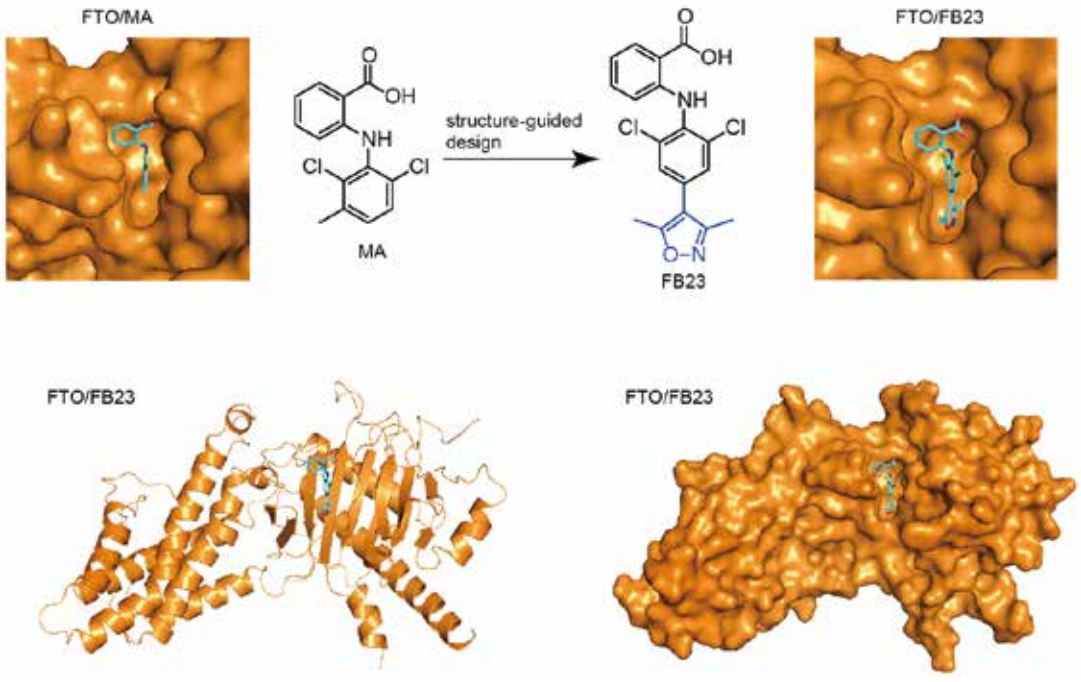
Scientists Provide A New Option for Anti-Leukemia Therapy

RNA epitranscriptomics, the study of chemical modifications to RNA or the transcriptome (the entirety of RNA in a cell), represents a recently identified layer of regulation of genetic information. As the most abundant internal mRNA modification, N^6-methyladenosine (or m^6A, adenosine tagged along with an additional methyl group) is critical for the regulation of mRNA metabolisms and impacts various biological and pathological processes.

The discovery of the fat-mass- and obesity-associated protein (FTO) as an m^6A demethylase corroborates the m^6A modification as a dynamic process. Recently, evidences prove that FTO is overexpressed in certain subtypes of human acute myeloid leukemia (AML) and promotes leukemogenesis. Thus, the development of effective inhibitors to target FTO's aberrant m^6A demethylase activity is in urgent need for leukemia therapy.

To address this urgent issue, Prof. YANG Caiguang's



Structure-based rational design from MA to FB23 yields selective inhibition against the oncogenic FTO demethylase (upper row); The FB22-FTO complex with FB23 sitting in the binding pocket of FTO are displayed in two different forms (bottom row). (Credit: YANG Caiguang, SIMM)

group from the CAS Shanghai Institute of Materia Medica (SIMM) has identified a potential therapy for AML by targeting the oncogenic RNA demethylase FTO through a joint study. The finding was published online in *Cancer Cell*.

Previously, Prof. Yang's team identified meclofenamic acid (MA) as a selective inhibitor of FTO demethylation over ALKBH5, the other m^6A demethylase. However, the activity and selectivity of MA limited its uses in the study of biological functions of FTO demethylase.

After years of efforts, scientists developed successfully two selective FTO inhibitors through structure-based rational designs and chemical synthesis, namely FB23 and FB23-2, which efficiently reverse/suppress FTO-mediated aberrant epitranscriptome in AML cells.

In line with the regulation of FTO on downstream target genes, FB23 and FB23-2 treatment increased significantly the ASB2 and RARA while decreased the MYC and CEBPA abundance in an m6A modification-dependent manner in NB4 and MONOMAC6 cells.

Moreover, FB23-2 displayed a favorable pharmacokinetic profile and exhibited therapeutic efficacy in treating mouse models grafted with patient-derived AML cells. Importantly, this proof-of-concept study has demonstrated that small-molecules targeting oncogenic FTO demethylase may be an effective therapeutic strategy for the treatment of AML.

However, due to the activity and selectivity of inhibitors, target engagement of current inhibitors needs further explorations. As FTO-mediated demethylation has also been linked to a variety of cancer types, the findings may have a broad impact on cancer therapy by targeting epitranscriptomic RNA methylation.

(SIMM)

Reference:

Y. Huang *et al.*, Small-Molecule Targeting of Oncogenic FTO Demethylase in Acute Myeloid Leukemia. *Cancer Cell* 35, 677 (Published: April 15, 2019). doi: 10.1016/j.ccell.2019.03.006.