Small-molecule targeting of oncogenic FTO demethylase in acute myeloid leukemia

With the support of the National Natural Science Foundation of China and the Chinese Academy of Sciences, the laboratory led by Yang CaiGuang (杨财广) from Shanghai Institute of Materia Medica, Chinese Academy of Sciences, has identified a potential therapeutic small molecule for treating the acute myeloid leukemia (AML) by targeting the oncogenic RNA demethylase FTO, which was published in *Cancer Cell* (2019, 35: 677—691).

In 2015, Yang's lab identified meclofenamic acid (MA) as a selective inhibitor of FTO demethylation over ALKBH5 by collaboration with Luo's lab at Shanghai Institute of Materia Medica and Jia's lab at Peking University. In 2017, Chen's lab from the University of Chicago reported that high levels of FTO demethylase result in pro-survival signaling in parallel with a block in differentiation in leukemic cells, which suggested the functional importance of FTO in AML pathogenesis. However, the cellular activity of MA still needs to be significantly improved in order to probe the biological impact of inhibiting FTO demethylases on human disease.

In this study, the scientists successfully developed two selective FTO inhibitors through structure-based rational design and chemical optimization, namely FB23 and FB23-2, which were shown to inhibit AML cell proliferation. More strikingly, both inhibitors were shown to increase differentiation of cells, thereby preventing AML propagation. Moreover, FB23-2 was shown to inhibit primary leukemia stem cells, thereby disrupting AML maintenance as well. FB23 and FB23-2 treatment mimicked the knockdown of *FTO* gene and significantly increased the ASB2 and RARA while decreasing the MYC and CEBPA protein abundance in an m6A modification-dependent manner in both NB4 and MONOMAC6 AML cells. Lastly, FB23-2 displayed a favorable pharmacokinetic profile and exhibited therapeutic efficacy in treating a patient-derived xeno-transplanted AML mouse model.

Epitranscriptomics is a rapidly evolving field in biology. Emerging evidence suggests that the deregulation of RNA methylation contributes to human diseases. Very few inhibitors for regulation of RNA methylation have been characterized and even less seems to be clinically applicable, however, which exists in sharp contrast to factors of DNA and histone epigenetics. This study provides a primary proof-of-concept that targeting epitranscriptomic RNA demethylase may be a new option for anti-leukemia therapy. As RNA demethylases have been related to various types of cancers, their findings will have an extensive influence on the cancer therapy by targeting epitranscriptomic RNA methylation in the future.

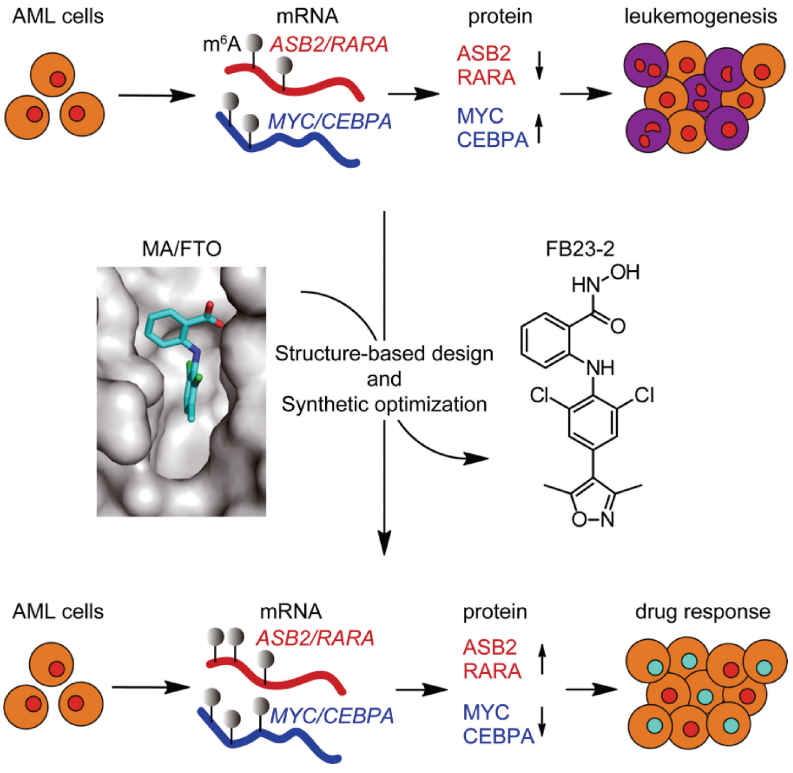

Figure Schematic diagram of small-molecular targeting of the oncogenic FTO demethylase.