Targeting Cancer with First-in-Class Inhibitors of the RNA m6A Methyltransferase METTL3

Oliver Rausch

Storm Therapeutics, Babraham Research Campus, Cambridge, UK
oliver.rausch@stormtherapeutics.com

METTL3 is an RNA methyltransferase which is responsible for the deposition of N-6-methyladenosine (m^6A) on selected mRNA targets, to regulate their stability and translation. We and others have recently shown that METTL3 is a promising therapeutic target for AML (Barbieri 2017). We have developed and characterised novel, selective small molecule inhibitors of METTL3, and used them to demonstrate their potential therapeutic utility to treat AML and solid tumors.

We identified chemical starting points for RNA methyltransferase inhibitors from both unbiased HTS and knowledge-based approaches using SAM analogs. Using structure-guided medicinal chemistry we developed and optimised potent and selective small molecule inhibitors of METTL3 from distinct chemical series. Structurally distinct compounds from different series were used to screen panels of cell lines derived from multiple solid and hematopoietic lineages. A broad range of anti-proliferative sensitivities of up to 100-fold was observed, with the most sensitive cell lines being of pancreatic, ovarian, lung and hematologic origins. Testing these inhibitors in a range of in vivo cancer models demonstrated profound efficacy in AML models, including AML PDX models, as well as inhibition of lung cancer xenograft growth.

Target engagement of METTL3 in cell lines and in vivo was confirmed by dose dependent depletion of m^6A on mRNA using mass spectrometry. In addition, multiple pharmacodynamic biomarkers of METTL3 inhibition were used to demonstrate METTL3 inhibition in these models.