Novel, small molecule PRMT5 inhibitors for treatment of cancer


SUMMARY

PRMT5, the major modulator of symmetric dimethylation of arginine (SDMA) has emerged as an attractive therapeutic strategy in various cancer types. PRMT5 over-expression (shown in several cancers including lymphoid, lung, breast, glioblastoma, gastric etc.) is thought to be an important factor in its tumorigenicity due to its repressive function on tumor suppressor gene expression. Therefore, inhibitors selectively targeting PRMT5 could be of high clinical value.

Structure based drug design was used to identify novel PRMT5 inhibitors. FlashPlatel methyltransfer assays, long term cell proliferation assays and symmetric dimethylation of known cellular protein SmD3 were used to assess in vitro potency and functional effect of PRMT5 inhibition.

A number of compounds from two different series showed strong in vitro potency against PRMT5, which were comparable to the reported GSK inhibitor, currently in Phase I. Multiple co-crystal structures have been solved in-house and extensively used in optimization of these novel scaffolds. JPRMT5i, a representative molecule showcased here exhibited a low nM potency both in vitro and cell based assays. A broad panel of lymphoma cell lines as well as a number of solid tumor cell lines (PDAC, SCLC and GBM) were sensitive to JPRMT5i. The compound exhibited good in vitro ADME properties in terms of aqueous solubility and metabolic stability and reasonable oral bioavailability in mouse pharmacokinetics. In Z-138 xenograft model, oral administration of JPRMT5i at 50 mg/kg resulted in complete (>99%) tumor growth inhibition and was tolerated well. At comparable dose, this tumor growth inhibition was better than the GSK inhibitor currently in Phase I. In addition, JPRMT5i showed reasonable brain exposure sufficient to achieve biomarker modulation in brain. In an orthotropic GBM model, JPRMT5i administration led to increased survival, normalization of brain weight, with no adverse effects on body weight.

In vitro characterization of JPRMT5i

JPRMT5i induces thermal shift in the presence of SAM

PRMT5 inhibition leads to G1-arrest and Caspase-mediated apoptosis

In vitro anti-tumor efficacy of JPRMT5i in Z-138 xenografts

In vivo anti-tumor efficacy of JPRMT5i in Z-138 xenografts

Modulation of PRMT5 targets in Z-138 xenograft mice brain

Conclusions

SAR has clearly demonstrated that there is further scope to optimize this series for potency, properties and brain exposure. Further studies are underway to better understand the therapeutic potential of these PRMT5 inhibitors in a number of solid cancers including PDAC, SCLC and GBM. Given the therapeutic importance of PRMT5 in multiple cancers, these molecules will be extremely valuable in treating this cancer either as standalone therapy or in combination with other standard of care agents.