INHIBITORS OF PROTEIN ARGinine METHYLTRANSFERASE 5

OVERVIEW

• Epigenetic target with cancer and non-cancer clinical potential (e.g. lung, mantle cell lymphoma; sickle cell disease, β-thalassemia).
• Tool compounds with in vivo PD biomarker modulation and good in vivo PK profile.
• Lead series of orally-available drug-like molecules with in vitro PD biomarker modulation.
• Established collaboration with world-leading PRMT5 research group.

Methyltransferases represent a novel area of drug discovery, albeit with strong precedents. CRT and CTx are seeking a commercial partner for collaborative research for the further development of these novel protein arginine methyltransferase 5 (PRMT5) inhibitors.

THERAPEUTIC OPPORTUNITY

Selective inhibitor of PRMT5 which would promote a pro-apoptotic response in cancer cells by modulation of p53. Likely oncology indications include mantle cell lymphoma (MCL), chronic lymphocytic leukaemia (CLL), melanoma and possibly lung, ovarian, breast, prostate, gastric, colorectal & cervical cancers. Haemoglobinopathy indications include sickle cell disease and β-thalassemia.

SCIENTIFIC RATIONALE

The protein arginine methyltransferase (PRMT) family of enzymes catalyses the methylation of specific arginine residues in proteins transduction, transcriptional regulation, RNA processing and DNA damage repair [1].

Haemoglobinopathies: Stephen Jane and colleagues have discovered that this activity of PRMT5 is critical in foetal globin gene silencing [2] and began the search for an inhibitor, since studies in patients with hereditary persistence of foetal haemoglobin (HPFH) have shown that elevated levels of foetal haemoglobin (to 20%) are sufficient to ameliorate the symptoms of β-thalassemia and sickle cell disease [3].

Tumourigenesis (Figure 1): PRMT5, a type II enzyme, symmetrically methylates the DNA regulatory proteins Histone H4 at arginine 3 (H4R3me2s) and Histone H3 at arginine 8 (H3R8me2s). PRMT5 has been shown to be essential for cell growth and to mediate E5 cell pluripotency [4]. Moreover, PRMT5 is involved in the transcriptional repression of tumour suppressors Rb, Nme1, ST7 and STAT3 and p53 [5,6,7]. PRMT5 expression is elevated in a number of cancers and is reported to correlate in some cancers with poor patient outcome e.g. breast5. Knockdown of PRMT5 has been shown to potentiate TRAIL-induced apoptosis in cancer cells [8], impair cellular response to hypoxic growth conditions by blocking the production of HIF-1α [9] and inhibit tumour growth in vivo in lung cancer xenografts [10]. PRMT5 was shown also to be necessary for cyclin D1-mediated cell transformation. Lymphoid tumours harbouring dysregulated cyclin D1 exhibit increased PRMT5-dependent histone methylation, associated with the loss of the cell cycle regulatory E3 ubiquitin ligase, CUL4 [11]. PRMT5 could be an excellent therapeutic target in cancers, and indeed the enzyme has been directly implicated in mantle cell lymphoma (MCL), chronic lymphocytic leukaemia (CLL), lung, breast, melanoma and may also be involved in ovarian, gastric, prostate, colorectal & cervical cancers [11,12,13].
CURRENT STATUS

Following a HTS campaign, numerous chemical series have been identified with drug-like physiochemical properties. Compound binding to PRMT5 has been confirmed by biophysical measurement and crystallography. A series of tool compounds has been optimised which shows excellent potency in cellular biomarker assays, good selectivity and dose-dependent modulation of a PD biomarker in vivo which has enabled significant validation of the project screening cascade.

Optimisation of three chemical series is currently in progress which are structurally distinct from the tool compounds, with the best examples showing IC₅₀ < 20 nM in cell-based biomarker assays and proliferation assays in combination with excellent in vitro metabolic stabilities (e.g. human liver microsome CLᵢ₅₀ < 7 µl/min/mg) and attractive early in vitro safety profiles. In vivo PK/PD and efficacy studies are currently in progress.

CTx has also developed protein expression systems, biochemical assays suitable for HTS, cell based models of PRMT5 function, and in vivo models.

PRMT5 LEAD SERIES

- Potent chemically tractable lead series in development.
- Good selectivity vs. a panel of methyl transferases.
- Target engagement in vitro (low nM range).
- Good physiochemical properties within series.
- Good microsomal stability.
- Good rodent PK and oral bioavailability within series.

PROPRIETARY POSITION

CTx’s proprietary position is composed of its collaboration with the world-leading research from the Jane group at Monash University, proprietary chemical matter, patent applications and a license to use the background IP developed by the Jane group. This includes, the know-how related to established molecular and cellular assays for PRMT5 and other methyltransferases, cellular and in vivo models.

REFERENCES


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