MONASH University

MONASH INNOVATION

POTENT INHIBITORS OF THE MOZ HISTONE ACETYLTRANSFERASE

A series of novel and potent inhibitors of the histone acetyltransferase monocytic zinc finger leukaemia protein MOZ (MYST3, KAT6A) with potential application in treating cancers.

- **Highly selective and potent (low nanomolar) small molecule inhibitors of the epigenetic drug target MOZ (KAT6A)**
- **Target genetically validated in a mouse model of B-cell lymphoma**
- ***In vivo* proof-of-concept studies underway**

THE CHALLENGE

MOZ (KAT6A), an oncogene and member of the MYST family of histone acetyltransferases, has key roles in promoting cell proliferation through transcriptional activation of negative regulators of the *Cdkn2a* locus, which encodes the tumour suppressors INK4A and ARF.

MOZ was originally identified in a recurrent chromosomal translocation, in aggressive myeloid leukaemia, fusing the MOZ gene to CBP. Other blood cancers involving MOZ fusion proteins have a poor prognosis, with a mean survival of less than 5 months. In addition, studies of copy number variations have shown that MOZ is located within the twelfth most commonly amplified genomic regions across all cancer types. **Thus inhibition of MOZ may provide a therapeutic benefit in a range of cancers.**

THE TECHNOLOGY

The Target

Studies have been performed to genetically validate the targeting of MOZ in cancer. In Eμ-Myc-transgenic mice, a widely-used model to investigate MYC-driven B-cell lymphoma, the loss of just one allele of MOZ increased the median survival by 4-fold (Fig.1). MOZ is also required to promote cell cycle progression and without MOZ function, cells enter permanent cell cycle arrest, or senescence[1] (Fig 2).

Table 1: Potency against MYST family

In-house HAT panel	IC_{50} (μM)
KAT6A / MOZ	0.008
KAT6B / Qkf	0.042, 0.020
KAT8 / MOF	28, 4.7
KAT2A / GCN5	>125
KAT2B / pCAF	>125
KAT3A / CBP	>125
KAT5 / TIP60	0.30, 0.13
KAT3B / p300	78, >125
KAT7 / Hbo1	0.37, 0.35

Further published work demonstrated that MOZ is required to maintain the proliferative capacity of B cell progenitors, even in the presence of MYC overexpression, by directly maintaining the transcriptional activity of genes required for normal B-cell development.[2] Taken together, these studies provide a strong rationale for targeting MOZ in blood cancer.

The Leads

Researchers led by Prof. Jonathan Baell from Monash Institute of Pharmaceutical Sciences and Assoc. Prof. Tim Thomas from The Walter and Eliza Hall Institute, have developed a series of novel and potent MYST family inhibitors.[3]

The Monash MYST family inhibitors are selective and have high affinity for MOZ (KAT6A) and MYST4 (KAT6B) (Table 1). Compounds have been co-crystallised with MOZ and numerous crystal complexes have been obtained at high resolution (1.8A˚).

Compounds have demonstrated activity in cell assays *in vitro* and *in vivo*, inhibiting the progression of MYC-driven lymphoma (Fig.2). In addition, treating mice with a MOZ inhibitor reduced B cell progenitor numbers without affecting total bone marrow cellularity. Thus, targeting MOZ is a promising therapeutic strategy, which offers the potential to extend survival in blood cancer and could be beneficial in a range of cancers.

Intellectual Property

National filings on PCT/EP2016/063125 claiming composition of matter and use in the treatment of cancers.

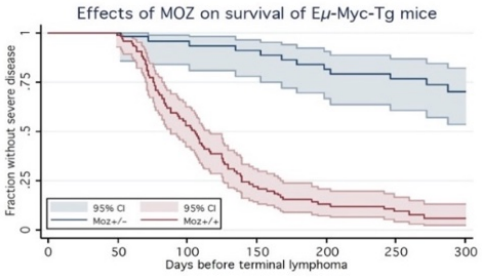

Figure 1: Kaplan-Meier survival curve of MOZ+/- versus MOZ+/+ mice.

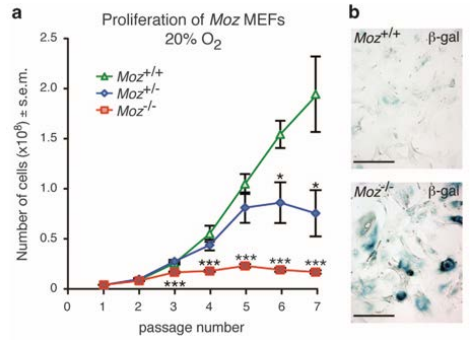

Figure 2: MOZ deficient cells undergo senescence independent of DNA damage.

References

1. Sheikh B *et al.* (2015) *Oncogene*. 34: 5807.
2. Sheikh B *et al.* (2015) *Blood*. 125: 1910.
3. Falk H *et al.* (2011) *J Biomol. Screen.* 16: 1196.

THE OPPORTUNITY

Monash seeks a license partner to co-develop its advanced lead series of MOZ inhibitors.

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