

## **EPZ015666, a PRMT5 inhibitor, selectively targets HTLV-1-infected T-cell lines *in vitro* and *in vivo***

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### **Background:**

HTLV-1 is the infectious cause of adult T-cell leukemia/lymphoma (ATL), an extremely aggressive and chemotherapy-resistant malignancy of CD4<sup>+</sup> T-cells. Many current therapies improve ATL patient survival, but the patients consistently relapse. Therefore, a need exists to identify novel targets relevant to the pathophysiology of ATL and innovative approaches to hit these targets. Protein arginine methyltransferase 5 (PRMT5) is a type II PRMT enzyme that has been directly implicated in the pathogenesis of multiple different lymphomas. Recently, our group found that PRMT5 is upregulated in HTLV-1-transformed cell lines, during HTLV-1-mediated immortalization, and in ATL patient samples. Here, we hypothesized that PRMT5 over-expression is relevant to HTLV-1-driven T-cell transformation and a commercially available inhibitor of PRMT5 activity (EPZ015666) would provide a novel approach to treating HTLV-1 malignancies.

### **Methods:**

A variety of HTLV-1-transformed cell lines, ATL-derived cell lines, and HTLV-1-negative T-cell lines were treated with EPZ015666 for 12 days. Cellular viability and apoptosis were measured by trypan blue exclusion and flow cytometry, respectively. Freshly isolated PBMCs were co-cultivated with lethally irradiated producer cells in the presence of titrating amounts of EPZ015666. Cellular viability and immortalization were measured over the course of 12 weeks. NOG mice transplanted with HTLV-1-transformed cells were treated with EPZ015666 and tumor burden, IL-2R $\alpha$ , and survival were measured over the course of 4 weeks.

### **Results:**

Inhibition of PRMT5 with EPZ015666 resulted in 1) a dose-dependent selective toxicity in HTLV-1-infected cell lines compared to HTLV-1-negative cells, 2) inhibition of HTLV-1-mediated T-cell transformation *in vitro*, and 3) increased survival and decreased tumor cell burden in HTLV-1-transplanted NOG mice *in vivo*.

**Conclusion:**

This study illustrates the significance of PRMT5 for the survival, transformation, and pathogenesis of HTLV-1, demonstrating the value of PRMT5 as a potential therapeutic target for ATL patients. Current studies to examine the mechanism of PRMT5 action are underway.

**Disclosure of Interest Statement:**

Nothing to disclose.

**Acknowledgement of Funding:**

This work was supported by the National Cancer Institute, P01CA100730.