Supplementary Figure 1. Selectively active epigenetic regulators in glioblastoma cells compared to other brain tumor entities. The G9a methyltransferase inhibitors UNC 0638, UNC 0642, and UNC 06446 were highly selective for glioblastomas (GBM) compared to the other tested entities (medulloblastoma (MB) and atypical teratoid/rhabdoid tumors (AT/RT)). The previously described inhibitor BIX 01294 showed no selectivity for GBM in our cross-entity screen. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

Supplementary Figure 2. Selectively active epigenetic regulators in atypical teratoid /rhabdoid tumor cells compared to other brain tumor entities. The DNA methyltransferase inhibitors 5-azacytidine and fisetin, as well as the jumonji inhibitor GSKJ4, were selectively active in atypical teratoid / rhabdoid tumors (AT/RT) compared to the other tested entities (medulloblastoma (MB) and glioblastoma (GBM)). *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

Supplementary Figure 3. The preferential anti-tumoral activity of HDACi in MYC-driven medulloblastoma cells. Dot plot demonstrating MYC-dependent preferential anti-tumoral activity of HDACi when medulloblastoma (MB) *in vitro* models were subdivided according to *MYC* status **, $p<0.01$.

Supplementary Figure 4. **In-Vitro Safety Profile of CI994**. In order to evaluate the potential safety profile of CI994 IC50 was evaluated for various normal or non-maligant cells. (A) Human fetal fibroblasts had significantly higher IC50 compared to Grp3-MB cells. (B) Cell viability was evaluated for normal human astrocytes (NHA) and mouse neonatal cortical neurons.

Supplementary Figure 5. **In vivo analysis of changes in protein expression after CI994 treatment.** Mice injected with D425 tumor cells expressing BFP-Luciferase were treated with CI994 as in figure 3, brain dissected out and regions of tumor isolated under a flourescence stereo scope. Tumors were dissociated into single cell suspensions and prepped for permeabelized with saponin and stained with anti-mouse CD45, anti-TGM2, anti-cMYC and anti-KI67. Tumor cells were identified as being msCD45-BFP+. Increase in cells expressing TGM2 (A) after CI994 treatment was observed while a significant decrease in MYC and Ki67 was observed (n=5 mice each)