

**An examination of the BET bromodomain inhibitor JQ1 in comparison with histone deacetylase & aurora kinase inhibitors in human cancers.**

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**Abstract #170664:**

**Background:** Up to 70% of human cancers overexpress MYC oncogenes, many via mutation, amplification or translocation, yet MYC has remained a challenging target for therapeutic intervention. MYC activation is associated with altered histone acetylation (HDAC) and the upregulation of aurora kinases (AK) (Gabay, Cold Spring Harbor, 2014). The BET bromodomain (BD) inhibitor JQ1 has been shown to downregulate MYC activity. **Methods:** We used a phenotypic platform to examine human tumor primary culture microspheroids isolated directly from patient surgical specimens to examine JQ1 activity in comparison with the activity of the HDACi, SAHA & 2 Aki’s, Alisertib & Tozasertib. Dose response curves generated by Ex Vivo Analysis of Programmed Cell Death (EVA-PCD) (Nagourney, Anticancer Res. 2012) were interpolated to provide LC50 values for comparison by Pearson Moment. **Results:** JQ1 reveals activity in human tumors with NSCLC, bladder cancer and Ewing’s Sarcoma falling in the sensitive range. Pearson Moment correlations, though preliminary, revealed the strongest correlation between JQ! And SAHA (r = 0.92) followed by Alisertib (r = 0.54) and Tozasertib (r = 0.24). **Conclusions:** BD inhibitors reveal activity in human tumors. Activity appears to differ by tumor type and between individual specimens within the same tumor types. Evidence of correlation with SAHA a pan-HDACi as well as the Aki’s suggests modes of action for JQ1 and may also offer potential strategies for future therapeutic interventions. Phenotypic platforms provide the opportunity to examine operative cellular signaling events in the presence or absence of detectable genomic alterations. As several HDACi’s are FDA approved and the Aki’s are in late stage clinical development, the entry of BD inhibitors into clinical therapy could offer the development of novel combinations and/or sequences of these drug classes. Additional studies are underway, as will be reported. Supported by the Memorial Medical Center Foundation and the Vanguard Cancer Foundation.