**Selective inhibition of BET bromodomains epigenetic signaling interferes with the bone-associated tumor vicious cycle**

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The vicious cycle established between bone associated tumors and bone resorption is the central problematic of the therapeutic strategies developed for primary bone tumors or bone metastasis. In this study we report data supporting BET bromodomain inhibition as a novel therapeutic strategy targeting simultaneously the three partners of the vicious cycle, using JQ1, a unique BET bromodomain inhibitor. A strong reduction of osteosarcoma cells viability and osteoblastic differentiation has been observed both in vitro and in vivo after BET protein inhibition associated to a transcriptional silencing of MYC and RUNX2 coincident with release of BRD4 from their respective locus. Moreover, we identified a BRD4-dependent RANKL activation of the NFATC1 transcription, leading to the inhibitory potential of JQ1 on osteoclast differentiation. This makes JQ1 a potent inhibitor of osteoblast, osteoclast differentiation and bone tumor development.