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Inhibition of Bromodomain Proteins in Treatment of Diffuse Large B-cell Lymphoma

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Title: Inhibition of bromodomain proteins in treatment of diffuse large B-cell lymphoma
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Only ~50% of patients with diffuse large B-cell lymphoma (DLBCL), the most common and aggressive subtype of non-Hodgkin's lymphoma, enter long-term remission after standard chemotherapy, and patients who do not respond to treatment have few options. Therefore, there is a critical need for effective and targeted therapeutics for DLBCL. Recent studies highlight the incidence of increased c-MYC protein in DLBCL and the correlation between high levels of c-MYC and poor survival prognosis of DLBCL patients, suggesting that c-MYC is a compelling therapeutic target for DLBCL therapy. The small molecule JQ1 suppresses *c-MYC* expression through inhibition of the BET family of bromodomain proteins. We show that JQ1 efficiently inhibited cell proliferation of human DLBCL cells regardless of their molecular subtypes, suggesting a broad effect of JQ1 in DLBCL. After JQ1 treatment, initial G1 arrest in DLBCL cells was followed by either apoptosis or senescence. In DLBCL cells treated with JQ1, we found that c-MYC expression was suppressed in the context of the natural, chromosomally-translocated or an amplified gene locus. Furthermore, JQ1 treatment significantly suppressed growth of DLBCL cells engrafted subcutaneously and improved survival of mice engrafted with DLBCL cells intraperitoneally. These results demonstrate that inhibition of the BET family of bromodomain proteins, and consequently c-MYC, has the potential clinical utility in DLBCL treatment.