Weill Cornell Medicine

Small Molecule BCL6 Inhibitors as Therapeutic Agents for B-Cell Lymphomas

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Background & Unmet Need

- Diffuse large B cell lymphomas (DLBCLs) arise from proliferating B cells transiting different stages of the germinal center (GC) reaction
- BCL6 is a transcriptional repressor involved in B-cell development
- BCL6 is also a key oncogene in many types of DLBCL, including GC B-cell (GCB)-DLBCL and Activated B-cell (ABC)-DLBCL, a class of DLBCLs that responds poorly to current therapies
- BCL6 is also expressed in follicular lymphomas (FL) and may be required for FL tumor cell survival
- Although protein-protein interactions are difficult to target with small molecules, BCL6 can be targeted via its highly specific BTB domain groove motif
- However, current BCL6 inhibitors are limited by their low binding affinity and therefore low efficacy
- **Unmet Need:** A small molecule inhibitor of BCL6 that is effective, specific, and non-toxic

Technology Overview

- **The Technology:** Small molecule inhibitor of BCL6 as a therapeutic candidate for B-cell lymphomas and other BCL6-dependent cancers
- In silico functional group mapping led to the design of improved small molecules which bind BCL6, disrupt formation of BCL6 repression complex, and induce de-repression of BCL6 target genes
- FX1 is highly specific, 10x more potent than endogenous co-repressors, and 100x more potent than the previous generation of BCL6 inhibitors
- FX1 enhances response to doxorubicin, including in chemotherapy-resistant ABC-DLBCLs
- **PoC Data:** Low, non-toxic doses of FX1 induced regression in 95% of established tumors in mice bearing GCB-DLBCL xenografts
- FX1 suppressed ABC-DLBCL cells in vitro and in vivo, as well as primary human ABC-DLBCL specimens ex vivo

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Patents:
US Patent 9,943,506

Publications:
Cardenas et al. *J Clin Invest.* 2016.
Hatzi et al. *Cell Rep.* 2013.

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Technology Applications

- Therapeutic agent for the treatment of B-cell lymphomas, such as DLBCL and FL
- Therapeutic agent for the treatment of other malignancies expressing BCL6
- Combination therapy with cytotoxic agents, including for chemotherapy-resistant malignancies

Technology Advantages

- Superior potency and efficacy at lower concentrations and without toxicity
- High specificity since FX1 binds the BTB lateral groove motif unique to BCL6 and not conserved in other BTB proteins
- Synergistic effect in combination with chemotherapy
- Favorable pharmacokinetics in vitro and in vivo
- High water solubility and good stability

Supporting Data / Figures

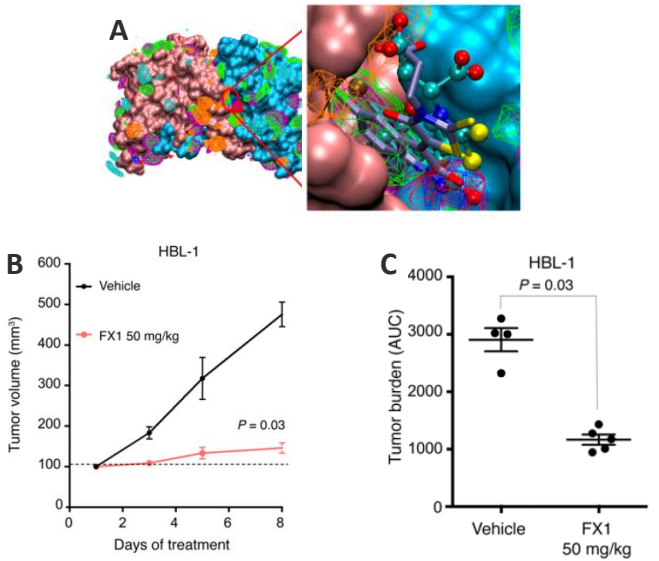

Figure 1: A. Identification of FX1 as a BCL6 inhibitor. **B, C.** FX1 suppresses DLBCL growth in mice with established xenografts, measured by reduction in tumor volume (**B**) and tumor burden (**C**).

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