

Novel BCL6 Inhibitor (FX1): Advances in Diffuse Large B-Cell Lymphomas (DLBCLs) Treatment

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To cite this article:

Md Kamrul Hasan. Novel BCL6 Inhibitor (FX1): Advances in Diffuse Large B-Cell Lymphomas (DLBCLs) Treatment. *Biomedical Sciences*. Vol. 3, No. 2, 2017, pp. 55-57. doi: 10.11648/j.bs.20170302.12

Received: November 25, 2016; **Accepted:** February 13, 2017; **Published:** April 26, 2017

Abstract: Diffuse large B-cell lymphomas (DLBCLs) are the most common and aggressive type of all the lymphomas. B cell lymphoma 6 (*BCL6*) oncogene is highly expressed in DLBCLs and one of the major reasons of treatment failure. Recent findings suggest that specific BCL6 inhibitor (FX1) disrupted formation of the BCL6 repression complex, reactivated BCL6 target genes, that in-turn suppressed growth of DLBCLs cells, primary human DLBCLs specimens, as well as induced regression of established tumors in mice derived from DLBCLs cells.

Keywords: Diffuse Large B-Cell Lymphomas (DLBCLs), BCL6, FX1

1. Introduction

Diffuse large B-cell lymphomas (DLBCLs) are an aggressive type of non-Hodgkin lymphoma that develops from the B-cells in the lymphatic system and accounts for 30%-40% of all cases. The disease is heterogeneous clinically, morphologically, molecularly; and characteristically exhibit poor prognosis [1]. There are two major biologically distinct molecular subtypes of DLBCLs: (i) germinal center B-cell (GCB-DLBCL) and (ii) activated B-cell (ABC-DLBCL). Although, the R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone; plus the monoclonal antibody rituximab) regimen remains the standard first-line treatment for patients with DLBCLs; however over 40% of patients relapse and die of their disease [2-5]. Patients with ABC-DLBCL observe more unfavorable clinical outcome as compared with GCB-DLBCL [6, 7].

BCL6 induces proliferation and survival of GC-B cells through repressing various checkpoint pathways, by recruiting the SMRT (silencing mediator for retinoid or thyroid-hormone receptors), NCOR (Nuclear Receptor Corepressor), and BCOR (BCL-6 corepressor) corepressors to its N-terminal BTB domain [8, 9]. The binding site for these corepressors consists of an extended groove formed through obligate homodimerization of BTB domains of BCL6, and mice expressing BCL6 with mutation in the corepressor-binding

groove fail to form GCs [10-12]. Moreover, translocations and amplifications of the B cell lymphoma 6 (*BCL6*) locus causes high expression BCL6 protein in ABC-DLBCL [13-15].

2. Results

Recently, Cardenas M. G. *et al.* identified FX1 as a specific BCL6 BTB inhibitor by using an in silico drug design functional-group mapping approach called SILCS, that has greater potency than endogenous corepressors and binds an essential region of the BCL6 lateral groove [16]. FX1 activity was then screened using a BCL6^{BTB}-GAL4 DNA binding domain luciferase reporter assay as well as Monte Carlo-SILCS (MC-SILCS)-ligand grid free energy (LGFE) analysis, and found that FX1 as the most active and selective BCL6 BTB inhibitor. Microscale thermophoresis (MST) analysis revealed that FX1 bound to BCL6 BTB domain with over 4-fold higher affinity than its natural corepressor SMRT, and over 18-fold greater affinity than previously reported BCL6 inhibitor 79-6 [17].

In reporter assays, FX1 exhibited 10-fold greater inhibitory activity against the BCL6 BTB domain compared to related BTB domain containing transcription factors, and biochemical enzymatic activity analysis showed that FX1 at concentration of 10 μ M inhibits 80% of BCL6 activity without significantly inhibiting other 50 kinases, confirming that FX1 binding is

selective to BCL6. By inhibiting BCL6 to associate with its corepressors, FX1 can induce BCL6 regulated target genes including *CASP8* (Caspase-8), *CD69* (Cluster of Differentiation 69), *CXCR4* (C-X-C chemokine receptor type 4), *CDKN1A* (Cyclin-Dependent Kinase Inhibitor 1A), and *DUSP5* (Dual Specificity Phosphatase 5).

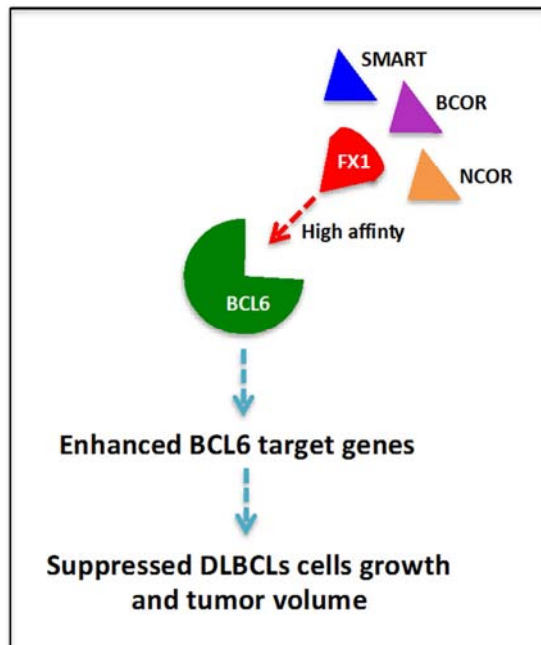


Figure 1. Schematic diagram of model for how FX1 can competitively bind to BCL6 and inhibit its corepressors such as SMART, BCOR, NCOR; that reactivate BCL6 target genes, which in-turn suppressed DLBCLs cells growth and tumor volume. Courtesy of Cardenas M. G. et al. (modified by M. K. Hasan).

In-vitro and in-vivo analysis revealed that FX1 showed a selective growth inhibition effect on BCL6-dependent GCB-DLBCL cell lines with average GI_{50} values of about 36 μ M, and FX1 caused profound and significant suppression of DLBCL xenografts in mice without exhibiting any toxic effects, and indeed not only prevented growth of the xenografts but in addition caused these tumors to shrink from their initial volume.

Although, ABC-DLBCL is relatively more resistance to CHOP plus rituximab (R-CHOP) therapy compared with GCB-DLBCL⁷; FX1 showed potential sensitivity to ABC-DLBCL cell lines with an average IC_{50} of 41 μ M and suppressed xenograft tumors derived from ABC-DLBCL cell line. Moreover, FX1 significantly decreased the survival of primary human DLBCLs cells including GCB-DLBCL and ABC-DLBCL origin. In addition, combined treatment of FX1 with the chemotherapeutic drug doxorubicin showed that FX1 enhances response to doxorubicin in GCB-DLBCL as well as the more chemotherapy-resistant ABC-DLBCL.

3. Conclusion

Overall results suggesting that FX1 might have potential applications for the treatment of patients with DLBCLs

including GCB-DLBCL and ABC-DLBCL.

Abbreviations

DLBCLs: Diffuse large B-cell lymphomas; BCL6: B cell lymphoma 6; GCB-DLBCL: Germinal center B-cell DLBCL; ABC-DLBCL: Activated B-cell DLBCL; R-CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; plus the monoclonal antibody rituximab; SMRT: Silencing mediator for retinoid or thyroid-hormone receptors; NCOR: Nuclear receptor corepressor; BCOR: BCL-6 corepressor; MC-SILCS: Monte carlo-SILCS; LGFE: Ligand grid free energy; CASP8: Caspase-8; CD69: Cluster of differentiation 69; CXCR4: C-X-C chemokine receptor type 4, CDKN1A: Cyclin-dependent kinase inhibitor 1A; DUSP5: Dual specificity phosphatase 5.

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