Investigation of FHD-609, a potent degrader of BRD9, in preclinical models of acute myeloid leukemia (AML)


Abstract

Acute myeloid leukemia (AML) is a complex disease with multiple subtypes, each characterized by unique clinical and molecular features, driving the need to develop targeted therapies which exploit specific vulnerabilities. Bromodomain-containing protein 9 (BRD9) is a component of the ncbAF chromatin remodeling complex and has been recently indicated as a strong dependency in AML (Weisberg et al 2022). It has been shown that inhibitors of BRD9 induce growth inhibition and expression of apoptotic makers in AML cell lines (Hohmann et al 2016; Zhou et al 2021). FHD-609 is a potent and selective BRD9 degrader that entered clinical trials for Synovial Sarcoma and SMARCB1 loss cancers. Herein, we profiled the in vitro and in vivo anti-proliferative effects of FHD-609 in AML cell lines. In addition, we set out to explore the MOAs and predictive biomarkers that are associated with BRD9 dependency in AML.

Key results

➢ FHD-609 potently degrades BRD9 in AML cells and led to a strong anti-proliferative effect on a subset of AML cell lines in vitro
➢ IRF8 high expression is a potential predictive biomarker that is associated with AML sensitivity to FHD-609
➢ FHD-609 treatment led to significant closing of chromatin with IRF8 motifs, and reduction of IRF8 protein levels in AML cell lines sensitive to FHD-609
➢ FHD-609 treatment demonstrated strong anti-tumor growth in both IRF8 high CDX and PDX models

Given these findings, future work evaluating the role of BRD9-targeting agents should consider exploring their utility in the IRF8-high expressing AML subpopulation

Figure 1. A subset of AML cell lines are sensitive to FHD-609, a potent and selective BRD9 degrader

<table>
<thead>
<tr>
<th>AML cell line sensitivity to FHD-609</th>
<th>AML cell line name</th>
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<tr>
<td>Sensitive</td>
<td>EOL-1, MV411, MOLM-13, MOLM-14, OCI-AML-2, OCI-AML-4, NOMO-1, ML-2, SHI-1, OCI-AML-3, KO-52, HNT-34, NRK-1, Kasumi-1, KO-52, SET2</td>
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<tr>
<td>Not Sensitive</td>
<td>AML-193, Kasumi-6, THP-1, HL60, CMK-15, GOM-1, SKM-1, HEL62.1.7, KG-1, OCI-AML-5, OCI-M1, TF-1, HEL, CMK115, KG-1a, P31,FUJ, OCI-M2, U937, SHI, M57E, N4, MUT28, Kasumi-2</td>
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A) A panel of 39 AML cell lines representative of broad genetic backgrounds were treated with FHD-609 for 10 days. CTG assays were performed at end-point, and a threshold for sensitivity was set at IC50 ≥20nM and growth inhibition ≥50%.

Figure 2. Identification of IRF8 as a strong individual predictor for AML cell line sensitivity to FHD-609

Figure 3. A subset of AML patients with diverse genetic backgrounds have high IRF8 expression

Figure 4. CDX and PDX of IRF8-high AML cells show strong response to FHD-609

References


(See references)