

Development of MYD88-targeting compounds for Myddosome disruption and selective MYD88 degradation

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Activating MYD88 mutations are prevalent in B-cell malignancies, including Waldenström macroglobulinemia (WM; 95–97%), primary CNS lymphoma (70–80%), activated B-cell diffuse large B-cell lymphoma (DLBCL; approximately 40%), and other B-cell cancers. Mutated MYD88 forms highly stable oligomers that recruit IRAK4 and IRAK1, triggering Myddosome pro-survival signaling. Knockdown of mutated MYD88 markedly impairs malignant-cell survival, and peptide-mediated disruption of MYD88 dimerization reduces NF-κB activation in MYD88-mutated WM cells. These findings support targeting the Myddosome through degradation of mutated MYD88 or disruption of Myddosome assembly.

We therefore initiated a fragment-screening campaign to identify compounds capable of targeting MYD88 and enabling the development of MYD88-directed proteolysis-targeting chimeras (PROTACs) and Myddosome disruptors. Through primary and secondary screening, we identified fragment hits that supported the development of compounds designed either to disrupt Myddosome assembly or promote MYD88

degradation. To evaluate Myddosome disruption and MYD88 degradation, we established complementary biochemical and cellular assay systems to measure MYD88 dimerization, degradation, allele selectivity, Myddosome integrity, downstream signaling, and lymphoma-cell survival. These efforts led to identification of the lead Myddosome disruptor DFCI-003-107. DFCI-003-107 decreased NF- κ B activation and demonstrated dose-dependent apoptosis, with EC₅₀ values of 1.25 and 1.76 μ M in MYD88-mutated BCWM.1 and TMD8 lymphoma cells, respectively. We also developed the lead MYD88-directed PROTAC DFCI-003-23, which preferentially degraded mutant over wild-type MYD88, with DC₅₀ values of 2.7 and 16.4 μ M, respectively. DFCI-003-23 demonstrated dose-dependent antiproliferative activity, with EC₅₀ values of 6.11, 4.73, and 2.76 μ M in MYD88-mutated BCWM.1, TMD8, and OCI-Ly3 lymphoma cells, respectively. DFCI-003-23 also induced apoptosis in primary WM cells, which was enhanced in combination with venetoclax, while sparing bone marrow CD19-negative mononuclear cells.

These studies demonstrate the feasibility of developing MYD88-directed disruptors and PROTACs through systematic fragment screening. This work establishes two complementary therapeutic strategies for MYD88-mutated B-cell malignancies: disruption of Myddosome assembly and preferential degradation of mutant MYD88.



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