

A Molecular Glue Selectively Degrades MYD88 L265P and Overcomes Drug Resistance in WM

Yong Li

Center for Molecular Oncology and Cellular Therapeutics, Children's Mercy Research Institute, Kansas City, MO

The MYD88 L265P mutation is the principal oncogenic driver in Waldenström's macroglobulinemia (WM) and is associated with constitutive NF- κ B activation, enhanced tumor cell survival, and therapeutic resistance. Although BTK inhibitors have significantly improved outcomes for patients with WM, acquired resistance remains an important clinical challenge. Direct and selective targeting of mutant MYD88 has remained elusive. We performed high-throughput screening of approximately 15,000 compounds to identify agents selectively active against MYD88 L265P-driven lymphomas. Candidate compounds were evaluated using viability assays, proteomics, CRISPR-Cas9 functional screening, biochemical analyses, and xenograft models. Drug activity was further assessed in ibrutinib-resistant WM and lymphoma models and in combination with the BCL2 inhibitor venetoclax. Our results identified Lasalocid A as a potent and selective inhibitor of MYD88 L265P-positive lymphoma cells. Treatment with this natural compound suppressed NF- κ B and STAT3 signaling, reduced viability, and induced apoptosis in MYD88 L265P-mutated cell lines while sparing MYD88 wild-type cells. Proteomic analyses revealed selective loss of MYD88 protein following treatment. Mechanistically, lasalocid A directly bound MYD88 L265P and enhanced its interaction with the E3 ubiquitin ligase RNF5, resulting in K48-linked ubiquitination and proteasomal degradation of the mutant protein. CRISPR-Cas9 screening confirmed RNF5 as a critical mediator of this effect. Biophysical and cellular studies demonstrated formation of a ternary complex involving MYD88 L265P, lasalocid A, and RNF5, supporting a molecular glue mechanism of action. We found that lasalocid A significantly inhibited tumor growth, reduced MYD88 expression, and prolonged survival in MYD88 L265P xenograft models without significant toxicity. Importantly, the compound retained activity in multiple ibrutinib-resistant WM and lymphoma models and produced superior antitumor effects compared with BTK inhibition alone. Furthermore, combination treatment with venetoclax demonstrated synergistic activity in vitro and in vivo, resulting in enhanced tumor suppression and survival benefits relative to either agent alone. In summary, lasalocid A represents a first-in-class molecular glue degrader that selectively targets MYD88 L265P through RNF5-mediated ubiquitination and proteasomal degradation. These findings establish proof of concept for direct degradation of mutant MYD88 as a therapeutic strategy and support further development of MYD88-targeted degraders for WM and other MYD88-driven B-cell malignancies, particularly in the setting of BTK inhibitor resistance.

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First Name: Yong

Last Name: Li

Email: yli4@cmh.edu

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