

Clarifying the translational potential of B-I09

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To the Editor - Inositol-requiring enzyme 1 (IRE-1) is a central regulator of the unfolded protein response (UPR), and inhibiting its activity is likely to be of benefit for treating diseases related to proteostasis. Hetz *et al.* recently published a Review Article in Nature Chemical Biology exploring pharmacological targeting of the UPR for disease intervention¹, in which they discussed the efficacy of the IRE-1 inhibitor B-I09 to induce leukemic regression without causing systemic toxicity in mouse models. They also pointed out a caveat that high concentrations of B-I09 were administered frequently using 100% DMSO as a carrier and suggested that this reduces the translational potential of B-I09. Representing the team leading to the development and optimization of B-I09 for clinical use, we believe that some of the features of the compound and the characterization of its translational potential require clarification.

B-I09 was developed as a prodrug to target the RNase activity of IRE-1, leading to the suppressed expression of XBP-1s². We have used chemical synthesis to tune prodrug stability within a series of B-I09 analogues and achieve spatiotemporal control of inhibitory activity³. Studies using B-I09 have been instrumental in validating the IRE-1/XBP-1 pathway as a therapeutic target in diseases. For instance, pharmacological inhibition of XBP-1s using B-I09 phenocopies genetic deletion of XBP-1s in mouse models of chronic lymphocytic leukemia, Burkitt's lymphoma and chronic graft-versus-host disease (cGVHD)^{2, 4, 5}. As demonstrated in ERAI reporter mice, B-I09 effectively blocks the RNase activity of IRE-1 in dendritic cells⁶. To the best of our knowledge, B-I09 is the only IRE-1/XBP-1 inhibitor for which published pharmacokinetic data has guided dosing in mice². The translational potential of B-I09 is highlighted by consistent results in suppression of XBP-1s in targeted cells and amelioration of diseased conditions in various preclinical mouse models^{2, 4, 5, 7, 8}. Importantly, B-I09 appears to impose no systemic toxicity in treated mice as documented in several preclinical studies^{2, 4, 5, 7, 8}.

Relative to other known inhibitors of IRE-1, B-I09 has demonstrated remarkable efficacy in multiple preclinical animal models and is well-tolerated *in vivo*. For these reasons, we believe that B-I09 has outstanding potential for translational application.

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