Identification of Irestatins: A Novel Class of Hypoxia Targeted Cancer Therapeutics

D. Feldman, A. C. Koong, The Center for Advanced Medicine, Stanford, CA

Background: We have previously shown in a variety of genetic models that X-box binding protein (XBP-1), a key component of the unfolded protein response (UPR), modulates survival under hypoxia and is essential for tumor growth. Targeting XBP-1 is a promising hypoxia/ER stress specific therapeutic strategy.

Materials/Methods: We screened a 66,000 compound small molecule library to identify specific inhibitors of XBP-1 activation. We developed a series of cell based assays to verify the initial “hits” identified on our high throughput screen. We also developed an in vivo bioluminescent tumor imaging assay to determine if compounds with promising in vitro activity had similar activity in vivo.

Results: We identified a small molecule, termed “irestatin” that potently inhibits activation of XBP-1 with an IC50 of 20 nM. This compound blocks activation of XBP-1 dependent reporter genes, endogenous XBP-1 splicing, and downstream activation of XBP-1 target genes. Furthermore, irestatin selectively sensitizes tumor cells to hypoxia without any toxicity to aerobic cells. Irestratin has no effect on IRE1 kinase activity and specifically inhibits its endonuclease activity. Treatment of tumor xenografts with this compound results in potent tumor growth delay and no significant normal tissue toxicity.

Conclusions: Irestatins define a novel class of hypoxia specific anti-cancer drugs. Mechanistically, these compounds work by blocking activation of XBP-1 through specific inhibition of IRE1 endonuclease activity.

Author Disclosure: D. Feldman, None; A.C. Koong, None.