RTI Prominent Publication Summary

SNX2112, a Synthetic Heat Shock Protein 90 Inhibitor, Has Potent Antitumor Activity Against HER Kinase-Dependent Cancers


Melanie Silinski

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Heat shock protein 90 (Hsp90) is a protein chaperone that plays an important role in cell transformation by regulating the conformational maturation and stability of various types of proteins, including those involved in tumor growth and maintenance. Inhibition of Hsp90 has thus emerged as a possible strategy for the treatment of advanced cancers. Several natural products, including the ansamycin geldanamycin and its derivative, 17-AAG, inhibit Hsp90 chaperone function by binding to an adenosine triphosphate (ATP) pocket in the NH2-terminal domain of the protein. However, the utility of these drugs has been limited by their hepatotoxicity, poor solubility, and poorly tolerated formulations.

To identify novel inhibitors of Hsp90, a compound library was screened against the purine-binding proteome to identify novel scaffolds that selectively bind to the ATP pocket of Hsp90. Specifically, a purine-based affinity resin was used to capture purine-binding proteins. Compounds that displaced Hsp90 family members from this column were identified and the protein “hits” sequenced by mass spectrometry (MS). Using this “proteome mining” technology, SNX-2112 was identified as a novel synthetic compound that selectively binds to the ATP pocket of Hsp90 family members. The SNX-2112 scaffold is unrelated in structure to any of the other known Hsp90 inhibitors.

In this study, we determined the pharmacodynamic and antitumor properties of SNX-2112 and its water-soluble and orally bioavailable prodrug, SNX-5422, in cell culture and xenograft models of human epidermal growth factor receptor (HER) kinase-dependent cancers. Results show that SNX-5422 and SNX-2112 exhibit properties and potency similar to—and, in some models, superior to—that of 17-AAG. SNX-5422 is rapidly converted to SNX-2112, which was found by MS to accumulate in tumors relative to normal tissues. Effects were seen at nontoxic doses, which could be delivered chronically on a daily or five-times-per-week schedule.

These data suggest that SNX-2112 (delivered as a prodrug) represents a novel inhibitor of Hsp90 with pharmacologic advantages over the natural product Hsp90 inhibitors. This finding forms the basis for the human clinical testing of this agent in patients with breast cancer and other advanced malignancies.

Link: http://clincancerres.aacrjournals.org/content/14/1/240.full.pdf