RTI Prominent Publications Summary

Discovery of Novel 2-Aminobenzamide Inhibitors of Heat Shock Protein 90 as Potent, Selective, and Orally Active Antitumor Agents

Huang, K.H., Veal, J.M., Fadden, R.P., Rice, J.W., Eaves, J., Strachan, J.-P., Barabasz, A.F., Foley, B.E.., Barta, T.E., Ma, W., **Silinski**, **M.A.**, Hu, M., Partridge, J.M., Scott, A., DuBois, L.G., **Freed**, **T.**, et al. (2009). Discovery of novel 2-aminobenzamide inhibitors of heat shock protein 90 as potent, selective, and orally active antitumor agents. *Journal of Medicinal Chemistry* 52 (14): 4288-4305.


Melanie Silinski


Tiffany Freed

Heat shock protein 90 (Hsp90) is a protein chaperone that aids in the folding, maturation, transport, and conformational stability of its client proteins, which play critical roles in tumor growth, proliferation, and survival. Inhibition of Hsp90 has thus emerged as a possible strategy for the treatment of advanced cancers. While some recent Hsp90 inhibitors have exhibited promising activity, a need remains for the identification of small molecule inhibitors with enhanced potency and improved pharmacokinetics.

To identify a novel class of Hsp90 inhibitors, a diverse compound library was screened against the purine-binding proteome to identify novel scaffolds that selectively bind to the ATP pocket of Hsp90. This technology is known as “proteome mining.” 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).

A new class of Hsp90 inhibitors unrelated to any previously known scaffold has thus been discovered. These indol-4-one and indazol-4-one derived 2-aminobenzamides showed strong binding affinity to Hsp90, and optimized analogues exhibited nanomolar antiproliferative activity across multiple cancer cell lines. Hsp70 induction and specific client protein degradation in cells on treatment with the inhibitors supported Hsp90 inhibition as the mechanism of action. Computational chemistry and X-ray crystallographic analysis of selected member compounds clearly defined the protein-inhibitor interaction and assisted the design of analogues. 4-[6,6-Dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(trans-4-hydroxycyclohexyl) amino]benzamide (SNX-2112) was identified as highly selective and potent (IC50 Her2 = 11 nM, HT-29 = 3 nM). A pharmacokinetic study was performed with its glycine ester mesylate prodrug (SNX-5422) and plasma samples were analyzed using a novel LC-MS/MS assay. SNX-5422 was orally bioavailable and efficacious in a broad range of xenograft tumor models (e.g. 67% growth delay in a HT-29 model) and is now in multiple phase I clinical trials.

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