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Hsp90 inhibitors: Past, present, and future

Hsp90 is a molecular chaperone that is responsible for the conformational maturation of more than 200 known substrates, many of which are associated with signaling pathways that are hijacked by transformed cells. As a result, Hsp90 has evolved into a promising anti-cancer target as multiple signaling nodes can be targeted simultaneously through Hsp90 inhibition. More than 15 small molecules that bind to the Hsp90 N-terminal binding pocket have entered clinical trials for evaluation against a number of human malignancies, but unfortunately, a lack of efficacy and/or toxicity has been observed for many of these candidates. In an effort to develop new strategies toward Hsp90 inhibition, we have focused on the development of isoform-selective inhibitors. Using a structure-based approach, we have produced the first isoform-selective inhibitor of Grp94, the Hsp90 homologue located in the endoplasmic reticulum. The design, synthesis, and biological properties manifested by Grp94-selective inhibitors will be described in this presentation.

Biography

Brian S. J. Blagg completed his Ph.D. from the University of Utah in 1999, followed by a postdoctoral position at The Scripps Research Institute. He is currently a Professor of medicinal chemistry at The University of Kansas and serves on several Editorial Advisory Boards for Medicinal Chemistry Journals and is an Associate Editor for the Journal of Medicinal Chemistry. The Blagg research Group has won several awards, including the 2009 American Chemical Society's David W. Robertson Award for excellence in Medicinal Chemistry.

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