

## INHIBITION OF HSP90 AS A SPECIAL WAY TO INHIBIT PROTEIN KINASES

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The 90 kDa heat shock protein (Hsp90), a ubiquitous molecular chaperone, specifically enables numerous protein kinases to maintain their activation-competent conformation. Hsp90 has an N-terminal nucleotide binding site, which includes a Bergerat-fold characteristic of bacterial gyrases, topoisomerase and histidine-kinases.

Numerous inhibitors have been developed to block ATP binding at this site of Hsp90, e.g. the ansamycin geldanamycin, or the structurally unrelated radicicol [1]. These drugs induce the dissociation and proteasomal degradation of many Hsp90 client proteins, including numerous serine/threonine and tyrosine kinases. Not surprisingly, Hsp90-inhibitors block T lymphocyte activation via the inhibition of kinase-dependent signaling steps, such as the Lck, or Raf kinase [2]. The Src-kinase inhibitor herbimycin-A also functions via this pathway. Many Hsp90-specific inhibitors are currently undergoing clinical trials as anticancer drugs:

Drug candidate Major effect Company and web-site Ref.

Geldanamycin analogues Hsp90 inhibition Conforma Inc. ([www.conforma.com](http://www.conforma.com)) [3]

Geldanamycin-testosterone Specific Hsp90 inhibition in tumors [4]

Radicicol Hsp90 inhibition Kyowa Hakko Kogyo Ltd. ([www.kyowa.co.jp](http://www.kyowa.co.jp)) [5]

Purine-scaffold Hsp90 binders, PU3 Hsp90 inhibition [6]

Our data indicate the presence of another nucleotide binding site on the C-terminus of Hsp90 [7]. This site opens up only when the N-terminal site has been already occupied by a nucleotide. Interestingly, a selective inhibitor of the C-terminal site is cisplatin, another widely used anticancer agent. Cisplatin has a different Hsp90-dependent kinase inhibitory pattern than geldanamycin, or other N-terminal Hsp90 inhibitors.

This may indicate a selective interaction of the two nucleotide binding sites with the adjacent chaperone sites, where kinases are bound and conformationally adjusted. The C-terminal nucleotide binding site favors GTP over ATP, which potentially enables a selective design of novel inhibitors against this site. The development of specific inhibitors against the C-terminal site may lead to the design of a novel class of protein kinase inhibitors with therapeutic benefit.

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