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Editorial Open Access

New Generation Cancer Drug Studies: Hsp90 Inhibitors

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Editorial

Heat shock protein 90 (Hsp90) is an ATP dependent highly conserved protein that provides client proteins to reach the correct conformation. Hsp90 uses ATPase activity to perform function such as folding for substrate proteins, misfolded protein degradation, cell cycle, and signal transduction [1,2]. Hsp 90 has 4 isoforms in the cell; inducible form Hsp90α and constitutive form Hsp90β in the cytosol, Grp94 in the endoplasmic reticulum and TRAP1 in the mitochondrial matrix. Hsp90 forms a homodimer and each monomer includes three domains: N-terminal domain (25 kDa) with a high ATP affinity co-chaperon binding site, middle domain (35 kDa) process client proteins, and C-terminal domain (12 kDa) has conserved EEVD motif and dimerization region. This homodimer forms a big hydrophobic cavity and this cavity encapsulates client proteins. This hydrophobic environment allows client proteins to fold their native structure. When Hsp90 dimer in open state, N-terminal domains protrude each other and upon client protein entrance the dimer closes around the client protein to provide a suitable hydrophobic place for folding. When ATP binds at high affinity state, dimer closes and ATP hydrolyzes and correctly folded client protein releases from the cavity [1-5] (Figure 1).

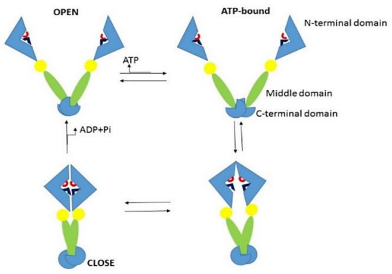

Figure 1: Hsp90 domains and ATPase cycle for folding client protein.

Typical client proteins are tyrosine kinases, metastable signaling proteins, mutated oncogenic proteins, steroid receptors, and cell-cycle regulators. And the client proteins are associated with Hsp90 chaperone function which play important roles in growth, proliferation, survival, and apoptosis of cancer cells (Table 1). Hsp90 significant role in cancer treatment because of Hsp90 inhibition provide degradation of oncogenic client proteins. This significant function of Hsp90 has made it important target in anti-cancer drug development [3,6,7].

Pathways	Client Proteins
Apoptosis	Akt, Rip, p53, Survivin, Apaf-1,Bcl2, IGF-IR
Growth signals	EGFR, Raf, Bcr-Abl, ErbB-2, Src, Akt,
Metastable signals	MMP-2, c-MET, HIF-1-α
Angiogenesis	VEGFR, HIF1, Akt, FAK, Src
Anti-growth signals	Plk-1, Cdk4, Cdk6, Myt-1, cyclin D

Table 1: Important oncogenic client proteins.

Cancer is a genetic disease that is the leading cause of death worldwide and is defined with six hallmarks by Hanahan and Weinberg [8]. New drug development efforts have been continued for cancer treatment. Cancer is a complex disease, some tumors in advanced patients has substantial complexity and biological heterogeneity. For this reason, novel drugs must be developed and using Hsp90 key function in folding client proteins researchers design Hsp90 inhibitors [7,9,10].

Hsp90 inhibitors are two classes; N-terminal domain inhibitors and C-terminal domain inhibitors as shown in Table 2.

N-terminal inhibitors		C-terminal inhibitors	
Inhibitor	**Derived from**	**Inhibitor**	**Derived from**
Tanespimycin (17-AAG, KOS953)	Geldanamycin	Chlorobiocin	Novobiocin
Alvespimycin (17-DMAG)	Geldanamycin	Coumermycin	Novobiocin
KF25706	Radicol		
KF29156	Radicol		
Cycloproparadicicol	Radicol		
PU3	Purine		
PU24hFCl	Purine		
PUS	Purine		

Table 2: Hsp90 inhibitors.

Approximately fifteen Hsp90 inhibitors are in clinic studies in various cancer types. Many of these inhibitors bind to N-terminal

domain ATP pocket that inhibit ATPase activity (Geldanamycin, radicicol, and purine derivates). But studies have directed to C-terminal domain as well due to toxic effect of N-terminal domain inhibitors. Hsp90 must be dimer form for carrying out the function. C-terminal inhibitors EGCG and novobiocin inhibit Hsp90 [2,11,12].

Drug designers try to find a better inhibitor for Hsp90 in terms of solubility and availability. Further, the researchers seek to find an inhibitor that will mimic the function of other complementary Heat Shock Proteins. A dual inhibitor that will block the function of Hsp70 will be an innovative form for this next generation drug candidates.

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