HSP90 and its inhibitors (Review)

HUIFANG HAO¹, YOSHIO NAOMOTO¹, XIAOHONG BAO¹, NOBUYUKI WATANABE¹, KAZUFUMI SAKURAMA¹, KAZUHIRO NOMA¹, TAKAYUKI MOTOKI¹, YASUKO TOMONO², TAKUYA FUKAZAWA¹, YASUHIRO SHIRAKAWA¹, TOMOKI YAMATSUJI¹, JUNJI MATSUOKA¹ and MUNENORI TAKAOKA¹

¹Department of Gastroenterological Surgery, Transplant and Surgical Oncology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University; ²Shigei Medical Research Institute, Okayama, Japan

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Abstract. The HSP90 molecular chaperone family is highly conserved and expressed in various organisms ranging from prokaryotes to eukaryotes. HSP90 proteins play essential housekeeping functions, such as controlling the activity, turnover and trafficking of various proteins, promoting cell survival through maintaining the structural and functional integrity of some client proteins which control cell survival, proliferation and apoptosis, and play an important role in the progression of malignant disease. HSP90 proteins are ATP-dependent chaperones and the binding and hydrolysis of ATP are coupled to conformation changes of HSP90, which facilitate client protein folding and maturation. Many natural and synthetic molecular compounds have been proposed as promising cancer therapy via disrupting the formation of complex ATP-HSP90-client proteins.

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1. Introduction

The HSP90 molecular chaperone family is highly conserved and expressed in various organisms ranging from prokaryotes to eukaryotes and even under normal conditions HSP90 proteins account for 1-2% of all cellular proteins in most cells (1). The expression of HSP90 is elevated up to 10-fold when exposed to physiologic stress including heat, heavy metals, hypoxia and low pH (2,3). HSP90 proteins play essential housekeeping functions, such as controlling the activity, turnover and trafficking of various proteins, promoting cell survival through maintaining the structural and functional integrity of some client proteins which control cell survival, proliferation and apoptosis (4,5). Many reports have indicated that HSP90 proteins play an important role in the progression of malignant disease and HSP90 expression is 2- to 10-fold higher in tumor cells than in normal cells (6-8). HSP90 sustains cancer cells through interacting smoothly with client substrates which contain kinases, hormone receptors and transcription factors directly involved in evoking multi-step malignancies, and also with mutated oncogenic proteins necessary for transformed phenotype (9). Therefore, HSP90 has been proposed as a promising target for therapy of various human cancers.

2. Structure and function

Researchers indicated that the HSP90 molecular chaperone family is present in the cytosol, nucleoplasm, endoplasmic reticulum, mitochondria and chloroplasts (1,10,11). Members of the human HSP90 chaperone family are listed in Table I. There are four kinds of isoforms, including HSP90α (90 kDa heat-shock protein), HSP90β, Grp94 (94 kDa glucose-regulated protein) and TRAP1 (tumor necrosis factor receptor-associated protein 1) (1,12). HSP90a and HSP90b are cytosolic proteins and share 76% homology due to gene duplication during evolution (11,15). Therefore, HSP90 has been proposed as a promising target for therapy of various human cancers.

Correspondence to: Dr Yoshio Naomoto, Department of Gastroenterological Surgery, Transplant and Surgical Oncology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata-cho, Okayama 700-8558, Japan
E-mail: ynaomoto@md.okayama-u.ac.jp

Abbreviations: HSP90, heat shock proteins; GA, geldanamycin; 17-AAG, 17-(allylamino)-17-demethoxy geldanamycin; 17-DMAG, 17-dimethylaminoethylamino-17-demethoxygeldanamycin hydrochloride; GIST, gastrointestinal stromal tumour; SAR, structure-activity relationships; (-)-EGCG, (-)-epigallocatechin-3-gallate

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The crystal structures of HSP90 proteins from *Escherichia coli*, yeast and human have shown that the basic domain is conserved, although it become more complex with multifunction from procaryote to eukaryote (19-24). Hsp90 chaperones exist as obligate homodimers, with each identical subunit comprised of an N-terminal domain, a middle domain, a non-conserved charged middle linker region which connects the N-terminal domain with the middle domain, and a C-terminal domain (19-24). There are two ATP binding sites, one is on the N-terminus and the other is on the C-terminus (25). The C-terminal domain contains a calmodulin binding site and dimerization site associating with its partner domain in the corresponding subunit to form dimer (1,18,26,27). A conserved pentapeptide sequence (MEEVD) lies in the extended C-terminal end of the eucaryotic protein, which serves as the primary binding site for tetratricopeptide repeat (TRP-a 34 amino acid sequence specifically binding to HSP90) domain containing co-chaperones (28-30). The middle domain of HSP90 exhibits a high affinity for co-chaperones and client proteins and seems to discriminate between different substrate types and to adjust the molecular chaperone for the proper substrate activation (31-35).

The crystallization and three-dimensional structure analysis of the N-terminal domain is a milestone in the scientific exploration of the HSP90 molecular chaperone family (21,23,36). Subsequently, the crystal structure of the HSP90-geldanamycin binding domain was reported to be a pocket which is also a likely binding site for the polypeptide substrate. So geldanamycin inhibits the HSP-catalyzed conformational reaction of these substrates via binding to the pocket (23). Another researcher group reported a different complex of crystal structures between the N-terminal domain of the yeast HSP90 chaperone and ADP/ATP comprised of a specific adenine nucleotide binding site homologous to the ATP-binding site of DNA, suggesting that geldanamycin works by blocking the binding of nucleotides to Hsp90 (21). A similar model was proposed in which the HSP90-geldanamycin binding domain is an ATP/ADP switch domain that regulates HSP90 conformation and the GA binding to HSP90 locks the chaperone into its ADP-dependent configuration (37). In subsequent years, it was established that Hsp90 is an ATP-dependent chaperone and the binding and hydrolysis of ATP are coupled to conformation changes of HSP90, which facilitate client protein folding and maturation and are disrupted by geldanamycin (38-42).

In recent years, more complex and detailed mechanisms of the ATP-driven chaperone cycle of HSP90 have been intensively explored. A crystal structure of complex with full length yeast HSP90 and an ATP analogue directly confirms that the N-terminal dimerization is necessary for the ATP hydrolysis which accompanies conformation change of client proteins (22). They further indicated that upon the ATP-bound state, the N-terminus and lid segment (residues 94-125) of the N domain and the catalytic loop of the middle segment together act as conformational switches to position the two halves of the catalytic apparatus for ATP hydrolysis (22). At the same time Buchner et al (2) proposed a model to explain how ATP hydrolysis is regulated and linked to conformational changes which is consistent with the crystal structure of full length yeast HSP90 and ATP. i) The stable structure of the first 24 amino acids and the lid region within the N-terminal domain preclude N-terminal dimerization; ii) upon binding of the ATP, this stable structure is opened, the dimerization site becomes accessible, and the N-terminal strands are exchanged with corresponding monomeric subunit to form the ATPase-active state; iii) after N-terminal dimerization, the positioning of the ATP-lid in its new orientation is required for the ATP-hydrolyzing reaction in this domain; iv) the association of the N-terminal domain with the middle domain of HSP90 is necessary for efficient hydrolysis (43).

Shiau et al further proposed a unified structurally validated mechanism model linking HSP90 ATPase activity and client protein binding and release. They indicated that a distinct set of lid segment conformation is responsible for coupling the nucleotide binding and hydrolysis to a cycle of domain rearrangements, which in turn regulate client-protein binding and release (19). i) Without the binding of ATP, HSP90 presents multiple hydrophobic elements into the central cleft, containing the hydrophobic patch formed by one face of the lid segment which in an inactive state as well as helix H1. The most hydrophobic surface area of the central cleft is supposed to be the most optimal for client-protein binding. ii) The ATP binding drives lid rearrangement and reorientation of the N-terminal domain and the middle domain, to which client proteins could be bound in the central cavity in this ATP-containing intermediate state of HSP90. iii) After rearrangement, the lid stabilizes N-terminal domain dimerization via interaction with N-terminal domain residues of the partner protomer and this ATP-mediated closing of the interprotomer space could very well drive client-protein remodeling. iv) With the dimerization of the N-terminal domain of subunits, the ATP hydrolysis occurs and the lid changes conformation accordingly, this new lid conformation allows the interdigitation of the lid, the src loop, and the CTD

<table>
<thead>
<tr>
<th>Protein</th>
<th>Subcellular location</th>
<th>Gene</th>
<th>Gene chromosomal localization</th>
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<tbody>
<tr>
<td>HSP90α</td>
<td>Cytosolic</td>
<td>HSP90AA</td>
<td>Chromosomes 1,3,4,11,14</td>
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<tr>
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<td>HSP90AB</td>
<td>Chromosomes 3,4,6,13,15</td>
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<tr>
<td>Grp94</td>
<td>Endoplasmic reticulum</td>
<td>HSP90B</td>
<td>Chromosomes 1,12,15</td>
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<tr>
<td>TNF receptor-associated protein</td>
<td>Mitochondria</td>
<td>TRAP</td>
<td>Chromosome 16</td>
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**Table I. Human HSP90 chaperone family.**
3. HSP90 inhibitors

Considering the extremely important function of HSP90 in organisms, especially in the occurrence and development of various tumors, targeting HSP90 is considered to have bright future. Through knowledge of the ATP-driven chaperone cycle of Hsp90, it might be possible to identify and design small molecule compounds which selectively affect the different stages of the cycle, thus providing more selective and effective therapeutics. In fact the exploring function of HSP90 is accompanied by the development of small inhibitors targeting HSP90, so far many kinds of HSP90 inhibitors have been identified which are listed in Table II and many of them have already exhibited good antitumor effects and have entered into clinical trials. The following will introduce the various kinds of natural and synthetic HSP90 inhibitors.

**Geldanamycin.** Geldanamycin (GA) is a kind of benzoquinone ansamycin antibiotic. As early as 1994, researchers proposed the ability of GA to revert the transformed phenotype of v-src-transformed cells via binding to HSP90 and disrupting its chaperone function (44). Subsequently, the identification of the ADP/ATP binding site in the N-terminal of HSP90 has driven the understanding of the inhibition mechanism of GA for cancer cells (21,23,36). GA competitively binds to the N-terminal ATP binding site of HSP90, which prevents ATP binding and disrupts the ATP-dependent conformational cycling reactions of a wide range of client proteins involved in signal transduction, cell cycle regulation and hormone responsiveness (21,23,38). Although GA exhibits potent antitumor effects, it also showed high hepatotoxicity and poor solubility in preclinical studies in animals, which has driven the development of geldanamycin analogues (45).

The tolerance at the 17-position for diverse substituents does not affect the formation of HSP90 and geldanamycin or its derivatives (47). So 17-allylamino-17-demethoxy-geldanamycin (17-AAG), the 17-position derivate of GA, was developed and has shown to have lower in vivo toxicity than GA with even less HSP90 affinity than GA (48). 17-AAG has promising antitumor effects in vitro and in vivo and has completed phase I clinical trials and is in phase II trials for several malignancies including metastatic melanoma, breast and ovarian cancer (49-52). However, poor water solubility makes formulation a barrier for its clinical application (53-55). Additional organic excipients such as dimethylsulfoxide (DMSO), polyoxylcastoroil (Cremophor) and egg phospholipida have been used as vehicles (53,56). However, these excipients may confuse the true maximum tolerated dose of 17-AAG and identification of the optimal dosing regimen in patients due to their own toxicities. With low doses of 17-AAG in DMSO, researchers did not get objective antitumor responses in several phase II trials including melanoma, hormone-refractory prostate cancer and renal cell carcinoma (52,57).

In addition, several characteristics of the chemical structure of 17-AAG have restricted fulfilling the maximal potential of its target in tumor cells (58). A benzoquinone moiety of the molecule has been related to the observed elevation of liver enzymes and liver toxicity in clinical trials. On the other hand, the expression of (P-gp) or loss or mutation of the NQO1 gene, which is necessary for the bio-reduction of 17-AAG, to the more potent hydroquinone have been proposed as mechanisms of de novo or acquired resistance to 17-AAG (58).

The difference between the 17-AAG and 17-DMAG is in the side chain at position 17 of the ansa ring (59). 17-Dimethyl-...
aminoethylamino-17-demethoxygeldanamycin hydrochloride (17-DMAG, NSC 707545) is a more potent, more water soluble derivative of 17-AAG and has potent inhibitory effects on cell proliferation in cultured tumor cell lines and in vivo xenografts, and is currently in phase I clinical trials (60,61). 17-DMAG can be administered orally, which possibly makes it a more feasible long-term therapeutic agent for treating disease (62). 17-DMAG is stable for at least 2 months at room temperature, less bound to plasma proteins compared to 17-AAG, and undergoes limited metabolism (53,62-64). Also, the limited metabolism of 17-DMAG compared to 17-AAG in preclinical models may reduce drug clearance and interindividual pharmacokinetic variability in humans (62,65).

IPI-504 is a highly soluble hydroquinone hydrochloride and novel analogue of 17-allylamino-17-demethoxygeldanamycin, which has >200 mg/ml solubility, thereby facilitating formulation for parenteral administration (55,66). The free base of IPI-504 is a potent inhibitor of HSP90, which exists in a dynamic intracellular equilibrium with 17-AAG (55,66). The half-life of IPI-504 is ~6 h in vivo, though significant accumulation occurs within tumor cells (66). Phase I trials of IPI-504 in patients with multiple myeloma (MM) and gastrointestinal stromal tumor (GIST) exhibited that the agent was well tolerated at doses up to 300 mg/m² (67).

Researchers have also synthesized other series of GA or 17-AAG by modification at the various positions. The C-11 modified analogues of GA and 17-AAG were identified with slightly improved cytotoxicity over 17-AAG against several cancer cell lines. The in vitro efficacy and pharmacological profiles of these compounds need further investigation to determine whether these compounds hold any advantages over 17-AAG (68).

**Radicicol**. Radicicol is a 14-membered macrolide originally isolated from *Monosporium bonorden* as an anti-fungal antibiotic in 1953 (69). Researchers found that radicicol has the ability to reverse the transformed phenotype in v-src, ras, mos, raf, fos and SV40-transformed cell lines to the normal cell cycle arrest in the G1 and G2 phase and inhibits angiogenesis in vivo (74). Crystal structure analysis has demonstrated that radicicol acts as a nucleotide mimic, inserting itself into the ATP/ADP-binding pocket of HSP90 (75). Other research groups also indicated that radicicol could bind to the N-terminal GA binding site of HSP90 protein with 50-fold greater affinity and thus destabilize its client proteins (76-78). Radicicol was found to show pot in vitro anti-proliferative activity against a wide variety of human tumor cell lines, but was inactive when tested against in vivo antitumor models (79).

Radicicol lacks in vivo antitumor activity because the inhibitory effect of radicicol against tyrosine kinases is abolished by reducing agents such as DTT, thus many novel series of derivatives of radicicol have been generated with better stability and biologic activity (71,80,81).

Oxime derivatives were developed and shown to be stable in the presence of thiol (81) such as KF25706, KF29518 and KF58333 were designed and synthesized and were found to show more potent anti-proliferative activities than radicicol and significant in vivo antitumor activities in several human tumor xenograft models (79,82). Researchers reported that KF25706 destabilized HSP90-associated molecules via binding to the HSP90 as radicicol in vitro and exhibited potent antitumor effects in vivo (79). KF58333, also a novel derivative of radicicol, was reported to bind to the Hsp90 chaperone machinery, deplete p210Bcr-Ab1 and Raf-1 proteins followed by induction of erythroid differentiation and G1 phase accumulation, and to induce apoptosis in human CML cells (80).

A new family of resocyclic macrolides was isolated from the fermentation of *Pochonia chlamydospora* and named pochonin A-F (83). Pochonin A is closely related to radicicol and was shown to be a 90-nm inhibitor of HSP90 (83). Pochonin C is also closely related to radicicol and can convert into radicicol (84).

**Radamide**. Based on the knowledge of co-crystal structures of the HSP90 N-terminal ATP-binding site with radicicol and GA, a chimeric inhibitor, radanamycin amide (radamide), was designed and synthesized via incorporating the key binding interactions provided by the resorcinol ring of radicicol and the quinone moiety of GA into a single molecule (75,85). Radamide exhibited low micromolar inhibition of HSP90 as measured by Her2 degradation in MCF-7 breast cancer cells (85). Chimeric compounds composed of radicicol’s resorcinol ring and GA’s quinone ring produce potent HSP90 inhibitors and further derivatives are likely to afford analogues with increased activity and perhaps useful alternatives to the geldanamycin derivatives in clinical trials (86,87).

**Novobiocin**. Novobiocin is a type of coumarin antibiotic isolated from *streptomyces spheroids*, which binds to the ATP-binding pocket of DNA gyrase thus eliciting antimicrobial activity via inhibition of ATP hydrolysis (88-91). Some studies indicated that the HSP90 N-terminal binding domain of GA and radicicol share homology to the bacterial DNA gyrase B protein adenosine triphosphate (ATP)-binding domain of novobiocin (21,23,37,77,92,93). Researchers began paying attention to the interaction of novobiocin and HSP90. Subsequently, Neckers et al reported that novobiocin binds to a site on HSP90 which is different from the GA/radicicol binding site and shows antitumor activity by reducing HSP90 client protein expression levels, such as p185erbB2, mutated p53, and Raf-1 in a dose-dependent fashion. They further proposed that the novobiocin binding domain is in the carboxy-terminal portion of HSP90 by using HSP90 deletion mutants (94). Ratajczak et al proposed that novobiocin antagonizes HSP90 function by inducing a conformation favoring separation of the C-terminal domains and release of substrate (95). However, the inhibitory effect was very poor within 500-800 μM in SKBR3 breast cancer cells (94). Thereafter, analogues of novobiocin with more potent inhibitory activity were developed.

In 2005, Blagg et al prepared a library of novobiocin analogues, which included shortening of the amide side chain and removal of the 4-hydroxy substituent, removal of both the 4-hydroxy and amide linker, steric replacements of both the 4-hydroxy and benzamide ring, and 1,2-positional isomers
of the noviosyl linkage. Among them, A4, which contains an \(N\)-acetyl side chain in lieu of the benzamide, lacks the 4-hydroxyl of the coumarin moiety, and has an unmodified diol, had a dramatic effect on the concentrations of the mutant androgen receptor, AKT, and Hif-1\(\alpha\) at a concentration of around 1 \(\mu\)M in the LNCaP cell line and drastically reduced levels of the androgen receptor at lower concentrations in a wild-type androgen receptor prostate cancer cell line (LAPC-4). A4 was identified to be a potent inhibitor of the HSP90 protein-folding process (96). They further explored the structure-activity relationships (SAR) for novobiocin and HSP90 and determined what modifications are necessary to convert a well-established, clinically used DNA gyrase inhibitor, novobiocin, into a selective inhibitor of HSP90. The 4-hydroxylation and the 3-carbamate were found to be detrimental for HSP90 inhibitory activity, but are critical for DNA gyrase inhibitory activity. According the SAR, they prepared the natural product derivatives, DHN1 and DHN2, which were selective for HSP90 and not DNA gyrase (97). The set-up of structure activity relationships for novobiocin and HSP90 are essential for exploring new coumarmycin analogues with better inhibitory activity and less toxicity.

In 2006, Blagg et al. developed dimeric variants of A4 exhibiting more inhibitory effective of dimeric natural product against Hsp90 protein folding machinery (98,99). A series of A4 analogues were prepared via linking A4 dimers by meta-and para-phthalic acid and utilizing the metathesis of olefins to generate a series of compounds that contained various methylene spacers in the tether (99). They found the more flexible derivative 33 dimers containing the olefinic linkers proved to be most active, which caused the degradation of HSP90-dependent substrates in a concentration-dependent manner without additional affect to the non-HSP90-dependent proteins. Further, they proposed that the geometry of the olefin responsible for dimerization is critical for inhibitory activity (99). Considering the structure-activity relationships (SAR), many other monomeric compound based on the A4 scaffold and the natural product novobiocin were developed (100). Two small molecule libraries were prepared and evaluated for anti-proliferative activity against several cancer cell lines. The first library explored optimization of benzamide containing a \(p\)-methoxy and a \(m\)-phenyl substituent and the second focused on the incorporation of heterocycles into the benzamide region in order to investigate hydrogen bond donor/acceptor interactions. Especially, 2-indoleamidine-46 was identified as the most potent inhibitor which inhibited cancer cell growth via inducing degradation of HSP90-dependent client proteins including Her2, Raf and Akt in a concentration-dependent manner (100).

In 2007, a parallel library of noviosylated coumarin analogues was envisioned according to the SAR, which aimed at HSP90 inhibition. Fifty-six noviosylated coumarin analogues were synthesized, omitting 4-hydroxy and 3-carbamate and providing additional hydrophobic and hydrogen bonding interactions by the incorporation of additional functionalities. Biological studies with these compounds are currently under investigation and the results from such studies will promote the development of optimized derivatives of coumarin with better inhibitory effects for HSP90 (101).

Another research group developed novel novobiocin analogues which lack the noviose moiety including those that connect the substituted coumarin ring to the aryl moiety through amide, retroamide, and alkylene linkage. The analogues labeled 6e and 6f were found to be more potent than novobiocin in the biological assay, such as by inhibiting of E2-induced and basal transactivation capacity of ERR, inducing a proteasome-mediated degradation of ERR, HER2, Raf-1 and cdk4, inhibiting the cell cycle, and promoting apoptosis and improving growth inhibition potential (102). Subsequently, they prepared the denoviose analogues bearing a tosyl group on the 4-position, with the removal of \(C7/8\) substituents, which exhibited increased inhibitory activity against the HSP90 protein folding process (103).

**Gedunin and celastrol.** Gedunin is a tetratranortriterpenoid isolated from the Indian neem tree, which exhibits anti-malarial, insecticidal and anticancer activity (107-109). Celastrol (tripetrine) is a triterpenoid from the celastraceae family and is extracted from *Tripterygium wilfordii* Hook F, and has shown anti-inflammatory and anti-proliferation effects in various cancer cells such as leukemia, gliomas and prostate (110-113). Gedunin and celastrol were identified to be HSP90 inhibitors via a connectivity map, a gene expression-based strategy (114,115). Gedunin and celastrol decrease the levels of a range of HSP90 client proteins and inhibit HSP90 activity itself in a cellular context directly or indirectly. Notably, gedunin and celastrol were found to inhibit HSP90 function by a different mechanism than existing N-terminal HSP90 inhibitors, thus they might act synergistically with existing modes of HSP90 ATP-binding site inhibition to inhibit HSP90 client signaling and viability in a cellular context (115). Subsequent studies reported that celastrol disrupted the protein-protein interaction of HSP90-Cdc3, resulting in the induction of HSP90 client protein degradation, which provides a novel mechanism for HSP90 inhibition against pancreatic cancer cells (116). Recently Sreraramula et al. proposed that celastrol inactivates Cdc37 by covalently binding to it or by forming either an intra- or intermolecular protein disulfide and the binding of celastrol induces large changes in conformation of the N-terminal kinase-binding domain and also the middle HSP90N-binding domain of Cdc37, thereby disrupting the Cdc37-Hsp90N complex which is crucial for stabilizing oncogenic kinases in various cancers (117).

**Derrubone.** The natural product derrubone was found to be a new HSP90 inhibitor by screening a large library of known...
of HSP90 inhibitors (131-133). The novel synthetic 3,4-diaryl pyrazole resorcinol inhibitor, CCT018159, was identified and showed potent antitumor activity in vitro (132,134). The structure-based design of CCT018159 generated a series of active pyrazole scaffold analogues, that display inhibition of cell proliferation similar to clinically evaluated 17-AAG. The crystal structure of the most potent new compound (VER-49009) bound to the target enzyme was determined and confirmed by experiment. VER-49009 binds to the ATP binding site of HSP90 with an IC50 of 25 nM in a fluorescence polarization (FP) assay and has anti-proliferative activity against HCT116 colon cancer cells, with a GI50 of 260 nM (135).

Subsequent structure-based design generated the significantly improved isoxazole resorcinol NVP-AUY922, which is currently under phase I/II clinical trials in cancer patients (136). NVP-AUY922 has excellent potency against HSP90 in an FP binding assay (IC50=21 nM), inhibits proliferation in a wide range of human cancer cell lines with an average GI50 of 9 nM and shows excellent efficacy in a range of subcutaneous and orthotopic human tumor xenograft models covering major cancer types and diverse oncogenic profiles. In addition, it is retained in HCT116 xenograft tumors at concentrations well above the GI50, with a half-life of 9.5 h following i.p. administration at 50 mg/kg qd (136). During its early clinical phases, it was considered that PET biomarkers could aid in the optimization of dosing and dose schedule (137).

SNX-2112. SNX-2112 is a newly developed HSP90 inhibitor that is unrelated to any previously known scaffold. The SNX-2112 scaffold was identified by screening the purine-binding proteome for non-quinone and non-purine-containing scaffolds that bind selectively to HSP90 and it is pan-selective for the HSP90 family in that it binds to Hsps90a, Hsps90B, Grp94 and Trap-1. A water-soluble prodrugs of SNX-2112, SNX-5542, was developed and showed improved solubility and pharmacologic properties due to the variable oral bioavailability of SNX-2112 (138). SNX-2112 and its prodrug SNX-5542 showed similar activity as 17-AAG, such as the degradation of HER2, mutant epidermal growth factor receptor and other client proteins; the inhibition of extracellular signal regulated kinase and Akt activation, and the induction of an Rb-dependent G1 arrest with subsequent apoptosis (138). Further study exhibited that SNX-2112 is highly potent against hematologic tumor cells via abrogating signaling which is dependent on Akt and Erk and induces tumor growth inhibition and prolongs survival in a murine xenograft model of human multiple myeloma (139,140). SNX-2112 is now in multiple phase I clinical trials.

STA9090. STA9090 developed by Synta Pharmaceuticals Corp. is a novel resorcinol containing a triazole compound unrelated to geldanamycin and acts as a potent HSP90 inhibitor (141). STA-9090 causes the degradation of multiple HSP90 client proteins, the killing of a wide variety of human cancer cell lines at low nano molar concentrations in vitro, and has shown potent anticancer activity in human xenograft tumor models (142). STA9090 is currently undergoing phase I or phase I/II trials (http://www.gistsupport.org/treatments/emerging-treatments/HSP90-inhibitors/sta-9090.php).
4. Conclusions

The HSP90 molecular chaperone family is highly conserved and expressed in various organisms ranging from prokaryotes to eukaryotes. HSP90 proteins play essential housekeeping functions and play an important role in the progression of malignant disease. HSP90 proteins are ATP-dependent chaperones and the binding and hydrolysis of ATP is coupled to conformation changes of HSP90, which facilitates client protein folding and maturation. Many natural and synthetic molecular compounds have been proposed as promising cancer therapies via disrupting the formation of complex ATP-HSP90-client proteins.

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126. NFL, NBA, MLB, NHL: 2007-2008 seasons.,