

Molecular Pathways: Targeting Hsp90—Who Benefits and Who Does Not

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Abstract

Many kinases and hormone receptors, important for cancer cell proliferation and survival, bind to and are dependent on the Hsp90 cycle for their folding and maturation. This provides the rationale for the development of small-molecule ATP competitors that, inhibiting Hsp90 function, lead to degradation of the "client" proteins. After continual efforts to improve the pharmacologic properties and the tolerability of these molecules, several Hsp90 inhibitors have exhibited activity in both preclinical models and in the clinical setting. As is the case with many other targeted agents, patient selection seems to be the major limitation to the success of these compounds. ERBB2-positive patients with breast cancer are exquisitely sensitive to Hsp90 inhibition. This is because ERBB2 is indispensable for growth and survival of this subtype of cancer, and at the same time ERBB2 is a client protein strictly dependent on Hsp90 for its maturation and stability. Extensive preclinical work identifying other ERBB-like client proteins will likely lead to the ability to enhance selection of appropriate patients for enrollment in more rational clinical trials. Hsp90 inhibition has also been reported to synergize with other therapeutic agents. Several ongoing studies testing different combinations of Hsp90 inhibitors with other targeted agents will confirm whether Hsp90 inhibition can potentiate the efficacy of targeted therapy and/or prevent the emergence of drug resistance. *Clin Cancer Res*; 18(17); 4508–13. ©2012 AACR.

Background

Hsp90 is a ubiquitous molecular chaperone required for correct folding and maturation of a variety of cellular proteins (1, 2). Hsp90, a protein that is highly conserved from bacteria to mammals, is documented to interact with more than 200 different "client" proteins (3, 4). The rationale that led to the development of Hsp90 inhibitors is as follows: (i) Hsp90 itself is reported to be specifically overexpressed in tumor cells (5–8) in a setting where it would also have more affinity for small-molecule Hsp90 inhibitors (9); (ii) Hsp90 client proteins are frequently oncogenes, mutated, or overexpressed, to which cancer cells are addicted for survival and proliferation (2, 10); and (iii) inhibition of Hsp90 leads to degradation of the client protein (11).

One of the Hsp90 client proteins is the progesterone receptor, which has been used extensively as a model to

understand the Hsp90 cycle (refs., 12, 13; Fig 1). Like the other client proteins, the progesterone receptor has no precise sequence consensus for the identification and recruitment (through the interaction with several cochaperones) into the Hsp90 cycle. In fact, the binding of each client protein seems to be conformational, related to a sequence contained in amino-acidic regions that encode a particular conformation (14–16).

The first step of the Hsp90 cycle is the binding between the cochaperone Hsp40 and the client protein. This interaction leads to the recruitment of ATP-bound cochaperone Hsp70, only weakly bound at this stage. The formation of this complex triggers ATP hydrolysis, which provokes a conformational change in Hsp70 increasing its affinity for the substrate (12, 17). ADP-bound Hsp70 can interact with Hop, an adaptor protein that simultaneously binds Hsp90 dimers, promoting the formation of an "intermediate complex" (18–21). ATP binding of the intermediate complex is also responsible for the progression to the next step of the Hsp90 cycle, again inducing a conformational change. ATP binds to Hsp90 dimers, forcing them to assume a "closed" conformation, which in turn facilitates the interaction with the cochaperone p23, and the dissociation from Hop (22–25). Subsequently, hydrolysis of ATP to ADP leads to disassembly of the complex and release of the mature client protein. These ATP-dependent conformational arrangements, crucial for the correct folding and consequent stability of the client proteins (26, 27), are the pharmacologic targets of small-molecule Hsp90 ATP competitors. Here, we describe several of the Hsp90 inhibitors currently in clinical development.

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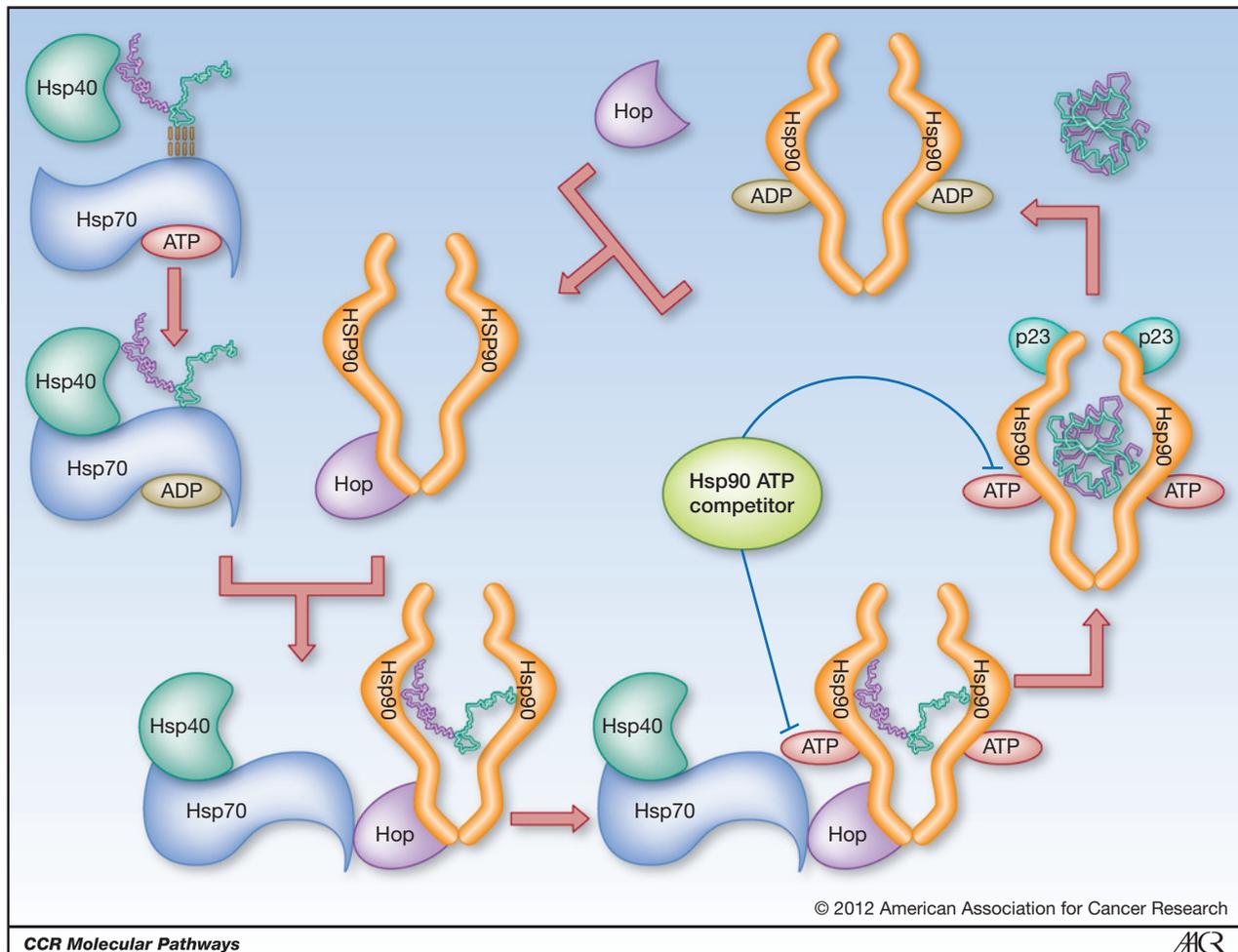


Figure 1. The Hsp90 cycle. Folding and maturation of the progesterone receptor is a model of how Hsp90 client proteins interact with Hsp90 and its cochaperones. The interaction between the cochaperone Hsp40 and the client protein leads to the recruitment of ATP-bound cochaperone Hsp70 that, following ATP hydrolysis, binds to another complex formed by the adaptor protein Hop and Hsp90 dimers. Binding of ATP to the Hsp90 dimers forces this intermediate complex to assume a closed conformation that facilitates the interaction with the cochaperone p23 and the dissociation from Hop. Hsp90 ATP competitors bind to the ATP-binding pocket of Hsp90 at this stage and impede hydrolysis of ATP to ADP, necessary for intermediate complex disassembly and release of the mature client protein. Nonmature proteins are rapidly degraded.

Hsp90 inhibitors

Geldanamycin derivatives. Geldanamycin is considered the prototype of the ansamycin class of Hsp90 inhibitors. Originally characterized as an antibiotic, this natural product showed intrinsic antitumor potential, inhibiting the activity of Src kinase by directly binding Hsp90 and interfering with the formation of the src–Hsp90 complex (28). Geldanamycin, however, was not clinically developed because of its poor solubility and substantial hepatotoxicity (29). These problems were overcome by its semisynthetic derivative 17-allyl-17-demethoxygeldanamycin (17-AAG), obtained by substituting a methoxy group for an allylamino group (30). This molecule was tested in more than 30 clinical studies, as a single agent or in combination with either chemotherapy or U.S. Food and Drug Administration (FDA)–approved drugs (31). Despite encouraging clinical activity, 17-AAG development was limited by its poor water solubility and, perhaps, by nonoptimal patient selection in the first trials. Progress in

development was achieved by converting the quinone ring of 17-AAG to the corresponding hydroquinone (IPI-504) by Infinity Pharmaceuticals. This modification significantly improved water solubility, facilitating pharmaceutical preparations (32, 33). *In vivo*, this molecule has the capability of shifting between the quinone and the hydroquinone form via redox equilibrium, with the hydroquinone form exhibiting more potent inhibition of Hsp90 (33).

Purines. In their search for synthetic molecules that compete with ATP for the Hsp90 ATP-binding pocket, Chiosis and colleagues identified PU3 as the first scaffold structure of this type having "geldanamycin-like" effects in breast cancer cells and from which more mature inhibitors were developed (34). PU-H71, an example from this research group, was found to be a potent Hsp90 inhibitor and was extremely efficacious in the preclinical models of triple-negative breast cancer. It is now being clinically evaluated in lymphomas (35). Conforma Therapeutics and

subsequently Biogen Idec later discovered BIIB021, a derivative of PU3, which is orally available and has significantly improved potency and pharmacologic properties. This molecule showed activity in a number of preclinical models and is now in clinical development (36, 37). Examples of purine-like inhibitors are CUDC-305 (38) and NVP-BEP800 (39). These agents are reported to have high oral bioavailability, increased tumor retention, and, in the case of CUDC-305, exquisite distribution in mouse brain tissue.

Resorcinol derivatives. Resorcinol is a natural antibiotic that competes with ATP for the binding to Hsp90. Resorcinol is a potent inhibitor of Hsp90 *in vitro* but, due to its intrinsic metabolic instability, lacks activity *in vivo* (40). With the use of alternate isolation techniques, other pharmacologically improved agents sharing the resorcinol core were identified by a number of research groups and/or pharmaceutical companies. Molecules such as NVP-AUY922, AT-13387, STA-9090, and KW-2478 have been described to be efficacious in several preclinical models and are all in different phases of clinical development (41).

Clinical-Translational Advances

As highlighted earlier, over the past decade our understanding of the function of Hsp90, together with the wealth of preclinical data validating Hsp90 as a pharmacologic target, has sparked interest in the development of Hsp90 inhibitors as a potential strategy for the treatment of cancer. A number of Hsp90 inhibitors are currently being tested in the clinic. In this section, we review the main cancer sites/subtypes where Hsp90 inhibitors are being investigated, the clinical data currently available, and the various strategies that are being pursued in optimizing their use in the treatment of cancer.

Clinically targetable client proteins of Hsp90

A number of malignancies in which Hsp90 inhibitors may have a potential role in treatment are currently being investigated. Estrogen and progesterone receptors are key drivers of breast cancer and are known to be client proteins of Hsp90 (12, 13). Furthermore, ERBB2, a receptor tyrosine kinase that is overexpressed in 20% of breast cancers, is also among the most sensitive client proteins of Hsp90, with shown preclinical activity of Hsp90 inhibitors in ERBB2-driven xenograft models (42, 43). In hormone-sensitive metastatic prostate cancer, androgen deprivation still is the mainstay of treatment and, given that the androgen receptor is a known client of Hsp90, inhibition of this chaperone may have a potential role in the management of this malignancy (44, 45). BRAF is mutated in 50% to 70% of malignant melanomas, and recent studies have shown that the use of BRAF tyrosine kinase inhibitors is associated with a survival advantage in this mutated subgroup (46). BRAF also depends on Hsp90 for folding and maturation, but, interestingly, Hsp90 inhibitors have been shown to selectively degrade mutant rather than wild-type BRAF (47). In principle, this property could also be exploited in colon cancer, where deregulation of the RAS/RAF/mitogen-acti-

vated pathway (48) and mutations of BRAF (49) are very well documented. However, the role of mutant BRAF in colon cancer seems to be less relevant than in melanoma. Other proteins that can potentially be targeted by Hsp90 inhibitors are mutant epidermal growth factor receptor, important in the treatment of non-small cell lung cancer (50), BCR-ABL, known to drive chronic myeloid leukemia (51), ZAP-70, associated with chronic lymphocytic leukemia (52), and CKIT, whose mutations drive gastrointestinal stromal tumors (53). Despite the fact that multiple myeloma does not depend on the classic client proteins described above, Hsp90 inhibitors are being actively investigated in this disease with the biologic rationale that Hsp90 is overexpressed in myeloma cells (54). Moreover, Hsp90 inhibition in this malignancy has shown activity in both *in vitro* and *in vivo* preclinical models through a proposed suppression of cytokine-dependent signaling pathways (55).

Single-agent activity of Hsp90 inhibitors

Although active as single agents, the natural Hsp90 inhibitors geldanamycin and resorcinol proved to be too toxic for clinical use. Tanespimycin (17-allylamino-17-demethoxygeldanamycin, 17-AAG), a derivative of geldanamycin, has been shown to have similar biologic activity as its progenitor, but with an improved toxicity profile. Tanespimycin has shown minimal to moderate activity as a single agent in a number of tumor sites including melanoma, breast cancer, prostate cancer, and renal cell cancer (56, 57). In heavily pretreated patients with multiple myeloma, it has shown a progression-free survival of 3 months among patients with minimal response and a progression-free survival of 2.1 months among patients attaining stable disease (58). Limited success of tanespimycin as a single agent has been attributed, at least in part, to lack of selection of patients most likely to benefit from the drug. In patients with trastuzumab-resistant HER2-positive metastatic breast cancer, the addition of tanespimycin to trastuzumab has been shown to be beneficial. However, the activity of the HSP90 inhibitor as a single agent in a subgroup of women with HER2-positive breast cancer was not studied. Avespimycin (17-dimethylaminoethylaminoethylamino-17-demethoxygeldanamycin, 17-DMAG), an analogue of geldanamycin, has been shown to have single-agent activity in a variety of solid tumors, including castration-resistant prostate cancer, chondrosarcoma, and renal carcinoma (59).

Use of Hsp90 inhibitors in combination with other therapies

Hsp90 inhibitors have shown superior effects when combined with a variety of other therapeutic agents. Perhaps the best example of this success is a recently reported phase II study of 31 patients with ERBB2-overexpressing metastatic breast cancer who progressed on trastuzumab-based therapy. They then received a combination of weekly tanespimycin and trastuzumab (60). The authors of this study reported an overall response rate of 22%, a clinical benefit rate of 59%, a progression-free survival of 6 months, and an overall survival of 17 months. Other interesting results

come from a subset of non-small cell lung cancer tumors driven by abnormal activity of the receptor tyrosine kinase, anaplastic lymphoma kinase (ALK), the target for the recently approved inhibitor crizotinib (61). In a recent report, Katayama and colleagues showed that non-small cell lung cancer cell lines that harbor the *ALK* gene translocation (responsible for ALK hyperactivity) and had become resistant to crizotinib retain sensitivity to the Hsp90 inhibitor tanespimycin (62). Moreover, single-agent retaspimycin hydrochloride (hydroquinone form of 17-AAG) has also shown activity in this subset of lung cancers (63).

BCR ABL, STAT3, and MEK, all client proteins of Hsp90, are (among others) important players in the progression of nonsolid tumors. Inhibition of the Hsp90 cycle has been shown to have synergistic activity in combination with proteasome inhibitors in the management of patients suffering from multiple myeloma (64, 65). In an open label phase I/II trial, Richardson and colleagues (66) reported an overall response rate of 27% with a complete response rate of 3% on a cohort of 63 patients with relapsed or relapsed and refractory multiple myeloma who received a combination of tanespimycin and the proteasome inhibitor bortezomib. Importantly, the authors further noted that this combination effectively inhibited both the proteasome (indicated by decreased 20S proteasome activity) and HSP90 (indicated by increased HSP70 expression).

Hsp90 inhibitors have shown either additive (67) or synergistic (68) activity also in combination with a variety of chemotherapeutic agents, including gemcitabine, carboplatin, docetaxel, and irinotecan (68–71). Significant activity has been also shown when Hsp90 inhibitors were combined with radiotherapy. Among the likely explanations for the observed synergy are enhanced antiangiogenic effects (72), the ability to compromise DNA damage response (73), and concomitant downregulation of ERB receptors (74).

Finally, preclinical evidence indicates that silencing the cochaperones Hsp70, Hsp27, or HSF-1 has been associated with increased sensitivity to Hsp90 inhibition. The activity of inhibitors of these cochaperones in combination with Hsp90 inhibitors is currently under investigation (75–79).

Designing the ideal clinical trial

Most of the clinical trials investigating the activity of Hsp90 inhibitors have been hampered by a variety of factors, including nonoptimal patient selection. It is possible that being driven by an oncogene client of Hsp90 is not a sufficient factor to predict clinical activity of Hsp90 inhibitors. Another possible determinant of activity of these agents will be the degree to which the client protein is dependent on Hsp90 for correct folding, maturation, and stability. Preclinical evidence indicates that ERBB2 is one of the most sensitive client proteins of the Hsp90 machinery. Clinical evidence indicates that breast tumors overexpressing ERBB2 that subsequently progress on trastuzumab still benefit by continued suppression of the ERBB2 pathway (80, 81). The activity shown by the combination of trastuzumab and tanespimycin (60), as described earlier, has

been similar if not superior to the combinations of multiple anti-ERBB2 agents. This successful therapeutic strategy was not serendipitous. The rationale for inhibiting Hsp90 in ERBB2-positive cancer cells arose from extensive preclinical work showing how this receptor relies on Hsp90 binding for its maturation, stability, and function. The lesson we may learn from this is that we should first have a strong indication that our "favorite target" really depends on Hsp90 for its activity before we design a clinical trial with Hsp90 inhibitors.

When it comes to designing clinical trials for combinations of Hsp90 inhibitors with other therapeutic agents, we may not have to be so strict about Hsp90 dependence of the client proteins. While therapeutic inhibition of an oncoprotein leads to silencing of the oncogene-dependent signaling, it has been recently observed that it also releases negative feedback, resulting in the activation of upstream receptors and parallel compensatory pathways that limits the efficacy of a given therapy (82). Blockade of these compensatory pathways may result in a "synthetic lethality-like" effect that would limit the emergence of both primary and acquired resistance to a variety of agents used in the management of cancer (82). It is likely that many client proteins of Hsp90 are among the key players/ effectors of these compensatory mechanisms and, as a result, the addition of Hsp90 inhibitors would be beneficial. With a systematic identification and characterization of the mechanisms that cancer cells devise to adapt to pharmacologic pressures, we will know whether the use of Hsp90 inhibitors is a valid combinatorial strategy in this setting.

Conclusions

It is becoming evident that being a client protein of Hsp90 does not necessarily mean being a "good" client. Only a fraction of the possible proteins interacting with Hsp90 are expected to serve as clinically exploitable targets. Careful and extensive preclinical work is needed to identify those client proteins that are indispensable for the growth and survival of a given tumor and, at the same time, those that are strictly dependent on Hsp90 for their maturation and function. Future combinatorial studies will confirm whether inhibition of Hsp90 is a good strategy to potentiate target inhibition and/or prevent the insurgence of drug resistance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interests were disclosed.

Authors' Contributions

Conception and design: M. Scaltriti, S. Dawood, J. Cortes

Development of methodology: J. Cortes

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Cortes

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Cortes

Writing, review, and/or revision of the manuscript: M. Scaltriti, J. Cortes

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Cortes

Study supervision: M. Scaltriti, J. Cortes

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