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Hsp90 inhibition: Elimination of shock and stress

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ABSTRACT

The 90 kDa heat shock proteins (Hsp90) represent a class of molecular chaperones responsible for the maturation and stabilization of many oncogenic proteins. Disrupting the ability of ATP to bind and facilitate the operation of Hsp90 has emerged as a promising approach toward cancer chemotherapeutic development. While numerous Hsp90 inhibitory scaffolds have been identified, progress through the clinic has revealed many obstacles that should be addressed in future analogue development. Recent reports of the complications, pitfalls, and downstream effects associated with Hsp90 inhibition are discussed herein, in hopes of providing a reference that can be used to guide the future design of Hsp90 inhibitory scaffolds.

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Within the last century, the inception of chemotherapy has revolutionized the treatment of neoplastic diseases. Although the concept of chemotherapy was developed in the early 1900s by Paul Erlich, surgery and radiotherapy remained the standard protocol for treatment of cancer well into the 1960s.^{1,2} Observations that cure rates obtained by local treatments had plateaued at ~33% expedited the investigation of new chemotherapeutic interventions.¹ Although an exciting time for drug development, much of the research was met with criticism and skepticism. Research during this time gave rise to the field of adjuvant chemotherapy; the application of drugs in conjunction with surgery and/or radiotherapy. This combined method for treatment has allowed for neoplastic therapies to be semi-personalized and has since become standard clinical practice.

The majority of currently used anti-tumor chemotherapeutics consist of natural product origins. These agents ascribe to various classes including microtubule stabilizers,³ microtubule disruptors,³ anti-metabolites,⁴ DNA alkylators,⁵ topoisomerase inhibitors,^{6,7} monoclonal antibodies,⁸ and anti-hormones.⁹ Although natural products remain the most widely used chemical entities for chemotherapeutic treatment, a strong movement towards the identification of small synthetic molecules exhibiting anti-neoplastic activity has emerged. The impetus for this movement is driven by the principles of medicinal chemistry, which includes improved pharmacokinetics, pharmacodynamics, solubility, toxicity profiles, resistance profiles, selectivity, and synthetic availability. Furthermore, small molecules provide access to structure–activity relationships (SAR) that are not feasible and/or easily accessed through natural product semi-synthesis.

Completion of the human genome project coupled with numerous scientific investigations have identified a myriad of molecular targets for clinical evaluation, resulting in new small molecule inhibitors that transition from an era of traditional chemotherapy to one of rationally designed drugs. Consequently, highly selective inhibitors of cellular machineries necessary for the survival of neoplasms have been identified; however, hurdles for such approaches still exist. Within the last 15 years, small molecule Hsp90 inhibitors have provided a new class of anti-neoplastic agents that are mechanistically distinct from other chemotherapeutics.^{10–15} Although Hsp90 inhibition represents a promising approach toward cancer; Hsp90 inhibitors also exhibit detrimental properties at present.

Hsp90 inhibition: The 90 kDa heat shock proteins, Hsp90, represent a class of molecular chaperones responsible for the stabilization, maturation, and re-maturation of numerous client proteins associated with oncogenic pathways. Inhibition of Hsp90 results in ubiquitination of the disrupted complex and subsequent degradation of the substrate protein via the ubiquitin–proteasome pathway.¹⁶ Many of the client proteins dependent on Hsp90 exhibit essential roles in the six hallmarks of cancer.^{17–19} Therefore, inhibition of Hsp90 results in simultaneous disruption of all six hallmarks, greatly reducing the potential for resistance to chemotherapeutic treatment.¹⁸

Two natural products, geldanamycin (GDA) and radicicol (RDC), have been identified as Hsp90 inhibitors and have played instrumental roles toward the generation of new small molecule Hsp90 inhibitors^{20–22} (Fig. 1). Although both natural products exhibit high potency in vitro, only GDA maintains activity in vivo. These two natural products have been utilized to identify other small molecules or semi-synthetic inhibitors of Hsp90,^{21,23} some of which have progressed into clinical evaluation.^{13,24–26} For compounds

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Table 1

Reported mutations to Hsp90 orthologs and the associated effects

Ortholog	Species	Mutation	Effect
yHsp82	<i>S. cerevisiae</i>	A107N	Stabilizes ATP lid closure; decreases efficacy of RDC and 17-AAG; ATP binding unaffected
yHsp82	<i>S. cerevisiae</i>	T22I	Decreases efficacy of 17-AAG; increases ATPase activity through Aha1 independent mechanism
Hsp90 α	<i>H. sapiens</i>	A121N	Stabilizes ATP lid closure; decreases efficacy of RDC and 17-AAG; ATP binding unaffected
Hsp90 α	<i>H. sapiens</i>	I128T	Decreases efficacy of RDC and 17-AAG in vivo; ATP binding unaffected; increases affinity for Aha1
Hsp90 β	<i>H. sapiens</i>	A116N	Stabilizes ATP lid closure; decreases efficacy of RDC and 17-AAG; ATP binding unaffected; increases affinity of Aha1
Hsp90 β	<i>H. sapiens</i>	I123T	Decreases efficacy of RDC and 17-AAG in vivo; ATP binding unaffected; increases affinity for Aha1
Hsp90 β	<i>H. sapiens</i>	T31I	Decreases efficacy of 17-AAG; increases ATPase activity through Aha1 independent mechanism
Hsp90	<i>H. fuscoatra</i>	L34I	Increased hydration state; decreases affinity for RDC; GDA and ATP binding unaffected

Table 2

Hsp90 co-chaperones and associated effects on the ATPase cycle

Co-chaperone	Effect
HOP/Sti1	Decreases ATPase activity through partial blockade of N-terminal nucleotide binding pocket; decreases efficacy of GDA and RDC
p23/Sba1	Binds to Hsp90/ATP complex, inhibiting ATPase activity; decreases efficacy of GDA and RDC
Aha1	Increases ATPase activity; decreases efficacy of GDA and RDC

sulted in dosing and scheduling conflicts in patients. In addition, various cell lines exhibiting an increase in drug efflux and metabolism have been reported to correlate directly with heat shock induction. Using photoaffinity labels, Benckekroun and colleagues demonstrated ansamycin analogs to act as both substrates and inhibitors of P-glycoprotein (P-gp) pumps, suggesting drug accumulation may be affected.³⁶ Identification of Hsp90 inhibitors that fail to activate the heat shock response and do not interact with P-gp pumps is important to the progression of Hsp90 inhibitor development. Elimination of these attributes will likely aid in the identification of amenable dosing and scheduling for oncology patients. Alternatively, strategies aimed at inhibiting Hsp90 and Hsp70 simultaneously or inhibiting the C-terminal nucleotide binding domain may represent promising avenues to mitigate some of the aforementioned problems with current inhibitors.^{41–43}

A myriad of partner proteins that interact with the Hsp90 machinery have been reported and it is well accepted that these co-chaperones work in collaboration to modulate the catalytic cycle.¹⁹ Alteration of the expression of these interactors has suggested yet another mechanism for acquired resistance to Hsp90 inhibition (Table 2). One example is the overexpression of p23/Sba1, which is responsible for binding to and stabilizing the Hsp90-ATP complex.³⁷ Upon stabilization, hydrolysis is blocked, and consequently the active site of Hsp90 remains occupied, eliminating the ability of inhibitors to modulate ATP binding. Consequently, Cox and Miller have demonstrated that overexpression of p23/Sba1 leads to lower responses to N-terminal inhibitors. Furthermore, Forafonov et al. reported that in the absence of p23/Sba1, cells are more responsive to Hsp90 inhibition.³⁸ Additional studies have shown that mutants of p23/Sba1 are viable, suggesting that p23/Sba1 interaction with Hsp90 may provide the first evolutionary mechanism designed to protect cells from Hsp90 inhibition.³⁹ In total, resistance to Hsp90 inhibition has been reported to arise through numerous mechanisms, and these mechanisms must be further elucidated and continually monitored during clinical studies.

Genetic polymorphisms: Apart from acquired resistance to Hsp90 inhibitors, intrinsically expressed genetic polymorphisms have also been identified. Two of these polymorphisms include DT-diaphorase and cytochrome P450 3A4 (CYP3A4). Although these polymorphisms seem to affect only certain ansamycin scaffolds, they deserve attention, as similar problems may arise with future Hsp90 inhibitors. Numerous polymorphisms of Hsp90 have been identified; however these polymorphisms usually result in diminished Hsp90 activity.^{44,45} For this reason, only genetic polymor-

phisms of the enzymes responsible for the metabolism of select ansamycin analogs are discussed herein.

Cytochrome P450 3A4 is one of the most active mixed-function oxidase enzymes in the human genome. In fact, CYP3A4/CYP3A5 are responsible for ~36% of xenobiotic metabolism and the CYP3A subfamily is the most abundantly expressed CYP in the liver (30%) and intestine (70%).^{46,47} Research has identified CYP3A4 as the enzyme responsible for the metabolism of 17-AAG.⁴⁸ Genetic polymorphisms of CYP3A4 are common, as over 40 single nucleotide polymorphisms have been identified in the CYP3A4 gene within the promoter and/or coding regions. The variability in this metabolic enzyme must be monitored during clinical evaluations of ansamycin-based inhibitors of Hsp90 as dosing and scheduling protocols may need to be changed. Furthermore, CYP3A4 is known to be inhibited and/or induced by many substrates, including currently used chemotherapeutic agents, antibiotics, immunomodulators and anti-depressants, all of which are commonly prescribed to oncology patients.^{46,47} Taken together, the genetic variability of the enzyme paired with the potential for serious drug–drug interactions suggests the development of small molecule inhibitors that lack interaction with CYP3A4 is important to the development of future Hsp90 inhibitors with clinical applications.

Outside of cytochromes P450 metabolism, research has shown the efficacy of 17-AAG to correlate directly with NQO1 gene expression in vitro.^{49,50} High expression of the NQO1 gene results in high levels of the DT-diaphorase enzyme, believed to be responsible for conversion of 17-AAG to a more efficacious hydroquinone, although the mechanism by which this occurs remains under investigation. Preliminary research suggests up to a ~32-fold increase in cellular sensitivity to 17-AAG in cells containing high levels of active DT-diaphorase. Intriguingly, this phenomenon was not observed for GDA or RDC, suggesting that this mechanism is not applicable to all Hsp90 inhibitors. Furthermore, the correlation between NQO1 expression and 17-AAG efficacy is not observed in vivo.⁵¹ The discrepancy between in vitro and in vivo dependence upon NQO1 expression should be considered when evaluating quinone containing Hsp90 inhibitors in preliminary biological evaluation. It is reported that 5–20% of the population is homozygous for the NQO1 2 polymorphism^{52,53} and DT-diaphorase expression in human tumors is known to be variable,^{54–56} suggesting that although dependence of 17-AAG on NQO1 has yet to be noted in vivo,^{51,57} subsequent quinone containing Hsp90 inhibitors should be evaluated for metabolic activation in vivo.

In total, the variability of CYP3A4 and DT-diaphorase polymorphisms suggests the need to determine the levels of these enzymes

and their effect on efficacy prior to administration of Hsp90 inhibitors. Furthermore, the ability to correlate enzyme effects *in vitro* and *in vivo* may help predict the efficacy and/or toxicity of inhibitors before administration. The design of inhibitors exhibiting activity independent of cytochromes P450 metabolism and intracellular reductases especially CYP3A4 and DT-diaphorase, respectively, will likely enhance the predictability and widespread use of Hsp90 inhibitors.

Downstream biological effects: The effect of Hsp90 inhibitors on the cell cycle and the mechanisms by which inhibitors induce cytostasis and/or apoptosis is well understood.^{12,14,58} However, recent research has shed light on unexpected biological events resulting from Hsp90 inhibition, leading to unanswered questions regarding downstream biological effects. It is well accepted that Hsp90 inhibition results in disruption of the Hsp90 protein folding machinery, inducing client protein degradation via the ubiquitin-proteasome pathway, resulting in eventual cell death. However, reports of downstream effects of Hsp90 inhibition are less understood and have only recently surfaced. For example, although previous research suggests intracellular Hsp90 inhibition to be anti-metastatic in nature,⁵⁹ Price and colleagues report that inhibition of Hsp90 with 17-AAG upregulates osteoclast formation and augments bone metastasis.⁶⁰ This is not surprising, as it was previously reported that 17-AAG exhibits pronounced effects on gene expression in cancer cells, including upregulation of genes responsible for tumor cell survival and/or growth in bone.⁶¹ Considering metastatic tumor growths cause the majority of deaths in cancer patients, and only ~20% of breast cancer patients survive longer than 5 years after bone metastasis is discovered,^{60,62} it provides an example as to why disease progression mechanisms must be further delineated.

Beyond specific disease progression, one must also look at the effects of Hsp90 inhibition on other tissues. Although the 'magic bullet' theory introduced by Erlich was intuitive, no such compounds have come to fruition beyond Gleevec. Non-selective binding and localization to non-diseased tissues have and will continue to cause undesired toxicities for chemotherapeutic agents. Evidence shows that Hsp90 inhibition significantly alters dendritic cell function by reducing T-cell proliferation and decreasing the ability of mature dendritic cells to present antigens.⁶³ Importantly, this data suggests that the Hsp90 protein folding machinery is essential to dendritic cell function and patients enrolled in Hsp90 inhibitor clinical trials should be carefully monitored for immunosuppression.

Another example of deleterious downstream effects resulting from Hsp90 inhibition is glomerular filtration as reported by Ramirez et al.⁶⁴ Multiple reports have established that Hsp90 is responsible for regulating nitric oxide (NO) synthesis, which is dependent upon endothelial nitric oxide synthase (eNOS).^{65–68} Due to the eNOS regulation on glomerular filtration rate, Ramirez and colleagues investigated the effect of acute Hsp90 inhibition with RDC on the eNOS pathway and glomerular filtration rate. The study suggests that RDC induced Hsp90 inhibition leads to decreases in eNOS phosphorylation, eNOS dimer/monomer ratio and in renal blood flow, therefore decreasing glomerular filtration rate, which can be associated with hypertension and metabolic syndrome.⁶⁴ Although eNOS is a known Hsp90-dependent client protein and such effects are not too surprising, these effects should be monitored during clinical evaluation of Hsp90 inhibitors.

Needless to say, further studies are necessary to determine the downstream biological effects of Hsp90 inhibition in order to anticipate potential complications that may arise in clinical trials. Future studies on the biology of Hsp90 inhibition will help identify potential side-effects including immunosuppression, hypertension, liver toxicity, and kidney failure.

Identification of proper Hsp90 inhibitory scaffolds: Although, cancer is commonly used to define a malignant growth or tumor

caused by uncontrolled cellular division, it is well accepted in the medical and scientific community that cancer is an umbrella term encompassing more than 200 diseases. It has been noted that each cancer exhibits a unique biological profile and distinct mechanism of progression. While the excitement surrounding Hsp90 research stems from the ability of Hsp90 inhibition to simultaneously disrupt all six hallmarks of cancer, many questions remain unanswered as to which cancer, which combination of therapies, and which patient population will be responsive to each Hsp90 inhibitory scaffold.

Until the recent advancement of various small molecule Hsp90 inhibitors into clinical trials, the majority of clinically relevant Hsp90 inhibitors have been ansamycin analogs. Efforts to improve upon synthetic feasibility, compound solubility, pharmacological profiles and physicochemical properties have inspired further small molecule development. Although all of the inhibitors in clinical trials bind and inhibit the ATPase activity of the N-terminal dimerization domain, each scaffold exhibits unique downstream effects and phenotypic changes in specific cancers. Reported structures of clinical candidates include purine, pyrazole–isoxazole and resorcinolic based scaffolds, however other structures have not yet been revealed.^{24,25}

Clinical results have shown Hsp90 inhibitory scaffolds exhibit unique efficacy profiles, suggesting specific scaffolds may be beneficial towards certain cancer types or that administration of multiple Hsp90 inhibitory scaffolds may act synergistically on malignant growths.^{24–26} Furthermore, it is apparent that Hsp90 inhibitory scaffolds may prevent the ability of malignancies to develop resistance to commonly prescribed chemotherapeutic agents,^{69,70} suggesting the identification of a combination therapy may represent the most promising strategy to treat patients. This has been affirmed in the clinic as the efficacy of monotherapy with specific Hsp90 inhibitors, especially ansamycin based scaffolds, has been a disappointment; however combinatorial therapies have been promising.^{24,25,70}

Identification of new Hsp90 inhibitory scaffolds and elucidation of each scaffold's biological profile will allow clinicians to more rapidly predict the proper indication and/or combination of therapies for each patient. Technological advancements now allow clinicians to screen for various biological markers and forecast disease progression, supporting the beginning of the era of personalized medicine.

Development of new Hsp90 inhibitory scaffolds and further evaluation of current scaffolds may also make it possible to identify isoform selective inhibitors. Identification of such inhibitors may prove beneficial in eliminating detrimental effects observed with *pan*-Hsp90 inhibition. Multiple isoforms of Hsp90 are found in the human genome and include Hsp90 α (inducible; cytoplasmic), Hsp90 β (constitutive; cytoplasmic), GRP94 (endoplasmic reticulum), and TRAP1 (mitochondrial). Each isoform may be responsible for the maturation of distinct client proteins. Thus, the ability to target one isoform selectively may enhance efficacy, therapeutic control and further elucidate the physiological role of each isoform. To date, little data exists suggesting isoform selectivity for any of the clinically relevant Hsp90 inhibitors. Identification of isoform selective inhibitors may allow for degradation of specific client proteins, which will further enhance selectivity and provide yet another class of Hsp90 inhibitors, potentially giving rise to a series of tunable chemotherapeutic agents.

Although the ability to identify Hsp90 inhibitory scaffolds is becoming trivial, understanding the biological responses inherent to each inhibitory class is difficult. Hsp90 has been validated as an anti-cancer target and clinical trials with various inhibitory scaffolds are ongoing.²⁸ Both academic and pharmaceutical research teams continue to invest resources in Hsp90 modulatory projects, however, the bottleneck for development of Hsp90 inhib-

itors remains focused on patient responses to Hsp90 inhibition and subsequent effects in gene expression levels.

Multiple Hsp90 inhibitory scaffolds have been identified and each scaffold appears to exhibit different binding modes and therefore different profiles of efficacy. Focus has shifted from semi-synthetic ansamycin analogs to scalable small molecules exhibiting superior physicochemical and pharmacological properties. The utilization of competitive small molecule Hsp90 inhibitors should provide tools that elucidate mechanisms and downstream biological effects resulting from the administration of each scaffold. Through collaborative efforts between medicinal chemists, pharmaceutical chemists and pharmacologists, new small molecule Hsp90 inhibitors will undoubtedly progress towards clinical evaluation. The continual development of novel Hsp90 inhibitory scaffolds paired with strong biological and mechanistic studies will help decipher the complicated network associated with Hsp90 inhibition and bring personalized chemotherapy to the forefront of medicine.

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