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# Pharmacogenomics in cancer drug discovery and development: inhibitors of the Hsp90 molecular chaperone

Paul Workman, PhD*

*Cancer Research UK Centre for Cancer Therapeutics, Institute of Cancer Research, Block E, 15 Cotswold Road, Sutton, Surrey SM2 5NG, UK*

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**Abstract**

Drug discovery is being revolutionised by a number of technological developments. These include high throughput screening, combinatorial chemistry and genomics. The impact of the new technologies is to accelerate the pace of anticancer discovery. The completion of the Human Genome Project and the ongoing high throughput sequencing of cancer genomes will facilitate the identification of a range of new molecular targets for drug discovery. Over the next few years we will have a complete molecular understanding of the various combinations of genes and cognate pathways that drive the malignant phenotype and tumour progression. The vision for postgenomic cancer drug discovery must be to identify therapeutic agents that correct or exploit each of these molecular abnormalities. In this way, it will be possible to develop personalised drug combinations that are targeted to the molecular make up of individual tumours. It is anticipated that these therapies will be more effective and less toxic than current approaches, although combinations of novel agents with existing cytotoxic therapies are likely to continue for some time. Examples of postgenomic, mechanism-based drugs include Glivec, Herceptin and Iressa, with many more agents undergoing preclinical and clinical development. An interesting new approach involves the development of inhibitors of heat shock protein (Hsp90) molecular chaperone. Because Hsp90 is required for the correct folding, stability and function of a range of oncoproteins that are mutated or over expressed in cancer, Hsp90 inhibitors have the potential to provide a simultaneous, combinatorial attack on multiple oncogenic pathways. By depleting the levels of multiple oncoproteins in cancer cells and blocking a wide range of oncogenic pathways, Hsp90 inhibitors have the potential to inhibit all of the hallmark characteristics of cancer cells. Progress in the preclinical and clinical development of Hsp90 inhibitors will be described, including an update on clinical studies with the first-in-class agent 17AAG. The use of the postgenomic technology of gene expression microarrays in cancer pharmacology and drug development will be exemplified.


*Keywords:* Pharmacogenomics; Hsp90; Molecular chaperone

## 1. Introduction: postgenomic drug discovery and development

New drugs for cancer treatment should ideally be more effective and less toxic than existing agents. With the completion of the Human Genome Project and the increased understanding of the abnormalities in the genomes of cancer cells, there are now many opportunities to exploit this knowledge to develop a new generation of rationally based, 'postgenomic' cancer drugs.

We have previously described a two-component strategy for the development of improved postgenomic cancer medicines [1,2]. This involves: (1) a focus on novel genes and molecular pathways involved in the molecular pathology of cancer to define new therapeutic targets and (2) the deployment of modern technologies to accelerate the pace of drug discovery. These technologies include molecular biology, genomics and bioinformatics; high throughput screening against structurally diverse, drug-like chemical libraries; combinatorial chemistry; rational design based on structural biology; cassette dosing for high throughput pharmacokinetics; molecular and imaging endpoints as pharmacodynamic markers of response; and pharmacogenomic biomarkers for use in the predictive individualisation of cancer treatments.

The recent impact of genomics on biology [3] and the development of new therapies [1,2,4–7] has been dramatic. The sequence of the human genome has been published at around 93% coverage [8,9]. Alongside the genome sequences of model organisms such as rat, mouse, fish, fly and worm, the human genome sequence provides a database which can be used to discover, and then understand the function of, all of the genes that are in existence. Figuring out the role of genes in various diseases is greatly facilitated. The identification

* Tel.: +44-208-722-4301; fax: +44-208-642-1140.
*E-mail address:* paulw@icr.ac.uk (P. Workman).

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of new targets for therapeutic intervention is accelerated. Large scale activities such as the Cancer Genome Project in the UK and the Cancer Genome Anatomy Project in the US will provide us with a complete description of the genomes of all human cancers and identify all of the genes that are involved in cancer causation and malignant progression [1,2,4–7,10].

A range of innovative therapeutic agents that are based on molecular oncology and cancer genomics are now demonstrating clinical utility in cancer patients [1,2,4–7]. The humanised monoclonal antibody Herceptin has been given regulatory approval for the treatment of erbB2 positive breast cancer patients and the bcr-abl tyrosine kinase inhibitor Gleevec (STI-571) was recently registered as a result of its remarkable activity against chronic myelogenous leukaemia. Following on, the EGF receptor tyrosine kinase inhibitor Iressa (ZD1839) is showing activity in non-small cell lung cancer and other tumour types. Additional promising targets include farnesyl transferase, cyclin-dependent kinases, the PI3 kinase pathway, histone acetylases/deacetylases, and also VEGF/HIF1-α signalling in angiogenesis.

The vision for postgenomic cancer drug discovery must now be to identify therapeutic agents that correct or exploit each of the molecular abnormalities and cognate biochemical pathways that are responsible for the initiation and progression of malignant diseases. Clearly, mechanism-based chemoprevention is also an important objective. The overall goal is to develop personalised drug combinations that are targeted to the precise molecular make up of individual tumours.

Inhibitors of the heat shock protein (Hsp90) molecular chaperone are of particular interest. This is a somewhat unusual example of postgenomic cancer drug discovery, since Hsp90 is probably not a cancer gene per se, but rather its protein product is required for the folding and functional activity of numerous cancer gene products. The concept of developing Hsp90 inhibitors for cancer treatment has been exemplified in animal models and has recently progressed to the stage of Phase I clinical trials with the first drug in this class [11]. In the rest of this article, the rationale for selecting this new molecular target will be assessed, recent progress will be described, and future prospects for the approach will be examined.

## 2. Hsp90: from heat shock protein to new cancer drug target

Molecular chaperones are responsible for maintaining the appropriate folding and three-dimensional conformation of proteins in the cell and are critical for controlling the balance between the synthesis and degradation of many proteins. Furthermore, they have been shown to play an important role not only in the stress response but also in regulating many critical cellular functions, such as cell proliferation and apoptosis [12–14].

Exposure of cells to environmental stresses results in accumulation of several chaperones, known as heat shock proteins (Hsps). This protective response is mediated by the transcription factor termed heat shock factor 1 (HSF1) and is known as the ‘heat shock response’ [15]. Of particular importance is that it is now clear that Hsps can also have a vital function under normal conditions by regulating the correct folding, degradation, localisation and function of a growing but nevertheless restricted list of important proteins (of which about 40 are currently known) that are defined as client proteins [11,12,16].

There is accumulating evidence that Hsps may play an important role in cancer and that Hsp90 in particular may be an important new target for therapeutic intervention [11,15,16]. Proof of principle has been demonstrated in animal models [17]. The promising results emerging from the Phase I trial with the geldanamycin analogue 17AAG (e.g. [18]) has stimulated considerable interest. Given the ability of Hsp90 inhibitors to block the growth of cancers containing a range of genetic and molecular abnormalities, it can be speculated that they will have broad-spectrum anticancer activity against many tumour types. In the wider context, it is interesting that a number of pathological conditions can be associated with abnormalities in protein folding, including Alzheimer’s and Creutzfeld-Jacob disease. Thus pharmacological modulation of protein folding and chaperone function could be considered to have much broader significance in a wide range of diseases [12,19].

## 3. Target validation for Hsp90

As mentioned, Hsp90 does not appear to be a cancer gene per se. Rather, the validation of Hsp90 as a promising molecular target in cancer comes from two convergent streams of investigation. The first involves molecular and biochemical studies that demonstrate a key role for Hsp90 in the activity of various oncogenic proteins and pathways. The second involves the demonstration that two classes of natural product have been found to cause inhibition of Hsp90 and that this explains their anticancer activity in animal models. The supportive experimental work in these two areas is discussed in more detail below.

Hsp90 and its endoplasmic reticulum homologue GRP94 are especially important for the correct folding, stability and biological activity of a set of client proteins that play an essential role in the cancer. These include c-Raf-1, Akt/PKB, erbB2, CDK4 and mutant p53 [16]. Additional client proteins include c-Src, c-Met focal adhesion kinase, polo kinase and the catalytic subunit of telomerase hTERT (e.g. [20,21]). It is clear that simultaneous depletion of these oncogenic clients should result in a powerful anticancer effect by interfering with all of the essential hallmark traits of malignant cells (Fig. 1 and see later in this section).

Although there is no evidence of Hsp90 mutation in cancer, there are several reports that suggest that Hsp90 and

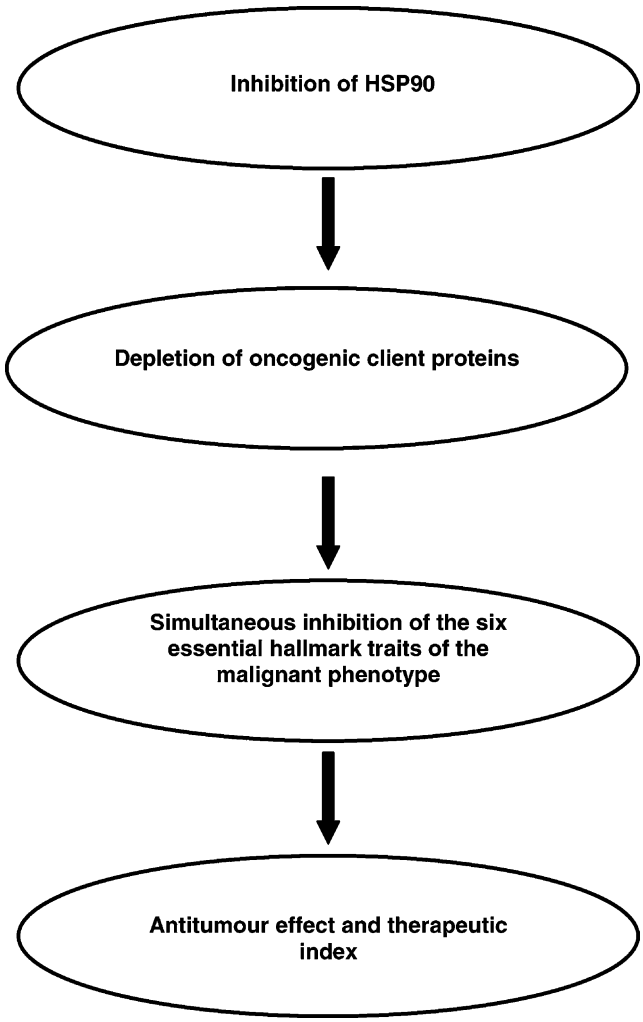


Fig. 1. Inhibition of Hsp90 produces an anticancer effect via proteosomal degradation of oncogenic client proteins, leading to simultaneous inhibition of the essential hallmark traits of cancer cells. For more details see Maloney and Workman [11].

other molecular chaperones may be overexpressed in malignant cells [11,22–28]. Hsp90 was identified by differential display and microarray analysis to be in a cluster of overexpressed genes that are associated with clinical stage in breast cancer [29]. Hsp expression has been reported to be an independent predictor of clinical outcome in prostate cancer [28].

Other important information supporting Hsp90 as a target for therapeutic intervention comes from biochemical and crystallographic evidence that this chaperone is the molecular target of two interesting classes of natural products that were already known to exhibit anticancer activity—these are radicicol and the benzoquinone ansamycins such as geldanamycin [30–33]. Both classes of agent interact with the nucleotide binding site in the N-terminal domain of Hsp90; this leads to inhibition of the ATPase activity that is essential for the molecular chaperone function [31,33,34].

Inhibition of Hsp90 leads in turn to depletion of client proteins in cancer cells, via the ubiquitin proteasome pathway [16,35,36]. For example, we have shown that Hsp90 inhibition results in simultaneous depletion of both the Ras → Erk pathway and the PI3 kinase pathway in human colon cancer cells, causing cell cycle arrest and/or apoptosis [36]. Simultaneous blockade of the effects of several genes that are critical for malignancy [37] provides Hsp90 inhibitors with the potential for a high level of activity against a broad spectrum of tumour types, to a large extent independent of their particular genetic make up. We have proposed (see [11] for details) that, as a result of the simultaneous blockade of multiple oncogenic pathways, Hsp90 inhibitors should be capable of inhibiting all six hallmark traits that constitute the malignant phenotype [38], including inhibition of proliferation/cell cycle progression, induction of apoptosis, and blockade of invasion, metastasis and angiogenesis (Fig. 1).

## 4. Anticancer activity and selectivity

Studies with geldanamycin showed that this agent had in vivo antitumour activity in animal models, but only at doses causing liver toxicity [39]. However, possibly due to differences in quinone metabolism that we have identified, (e.g. [17,40]) the 17-allylamino-17-demethoxy analogue of geldanamycin (17AAG; see Fig. 2) gave large growth delays at doses which had no toxic effects. 17AAG has activity against human colorectal and ovarian tumour xenografts [17,41] and additional data on xenograft models are held on file at the US National Cancer Institute.

It is essential to identify genes involved in sensitivity to Hsp90 inhibitors such as 17AAG, as well as to search for pharmacodynamic endpoints and biomarkers that are predictive of response. To this end, we used the powerful postgenomic technology of cDNA microarrays [42] to identify genes that show altered expression following inhibition of Hsp90 by 17AAG [35]. Various studies from our laboratory and elsewhere have also demonstrated depletion of individual client proteins (e.g. [36,43]). Using these methods, we have proposed a molecular signature that is diagnostic of Hsp90 inhibition. This involves depletion of client proteins such as c-Raf-1, CDK4 and Lck and simultaneous upregulation of Hsp70 genes. The assay can be applied to tumour cells and tissue, and also to peripheral blood lymphocytes [35,41]. Using these markers, we have shown that the antitumour activity seen in human tumour xenografts is consistent

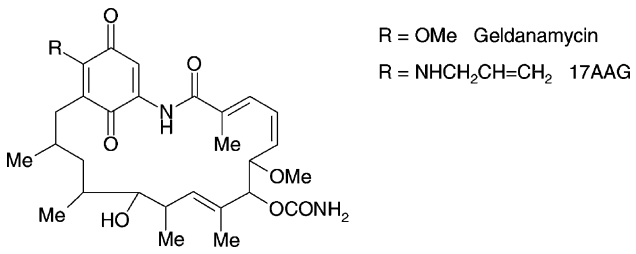


Fig. 2. Chemical structures of geldanamycin and 17AAG.

with the proposed mechanism of Hsp90 inhibition [17,41]. These endpoints are now being used in our clinical trial of 17AAG (see Section 5).

It is clear that 17AAG shows promising anticancer activity via the desired mechanism and that these effects are seen at doses that are not toxic to normal tissues (e.g. [17]). It is interesting to speculate on why a therapeutic window is apparent with Hsp90 inhibitors. Some possibilities are listed below. For a more detailed discussion see [11].

- We have suggested that the principle mechanism of cancer selectivity may involve simultaneous inhibition of oncogenic pathways (e.g. Ras → ERK and PI3 kinase) upon which malignant cells have become dependent [11]. In addition, simultaneous effects on the various hallmark traits of cancer (e.g. uncontrolled cell cycle progression, unlimited proliferative potential, evasion of apoptosis, invasion, angiogenesis, metastasis) will provide combinatorial effects on tumour versus normal tissue [11].
- It is conceivable the proteasomal machinery may already be overloaded in cancer cells as a result of the overexpression and mutation of oncogenic client proteins. Thus the additional stress that is induced by Hsp90 inhibitors may cause overload of the proteasome in cancer cells, leading to selective action versus normal cells.
- Fascinating studies have shown that Hsp90 may play a key role in 'morphological evolution' by buffering against the effects of mutations [44]. An ever-present feature of cancer cells is that they contain large amounts of genomic damage. Hence it can be speculated that inhibition of Hsp90 could result in the unmasking of potential synthetic mutations that provide further selective damage to cancer versus normal cells. The concept of synthetic lethality has been much discussed as a route to the selective therapy of cancer, and it is tempting to speculate that Hsp90 inhibitors may represent the first example of success.
- Finally, 17AAG has been reported to concentrate to a greater extent in tumour versus normal tissue. This pharmacokinetic effect, which may involve binding to the high levels of Hsp90 in tumour tissue, may also contribute to the tumour selectivity of the drug.

## 5. Current clinical status of 17AAG

Hsp90 inhibitor development is at an exciting stage with the entry of 17AAG into Phase I clinical trials in cancer patients at our own institution and at four institutions in the US. Initial results are encouraging (e.g. [18]). Concentrations greater than those needed for activity in vitro and in animal models have been achieved in the plasma of treated patients. Also, using the pharmacodynamic endpoints discussed earlier that define the molecular signature of Hsp90 inhibition, i.e. increased expression of Hsp70 and simultaneous depletion of client proteins, such as c-Raf-1 and CDK4, we have obtained clear evidence that the intended target is being inhibited in the peripheral blood lymphocytes and tumour tissue from treated patients. It is also clear that 17AAG is fairly well tolerated, although there is evidence of hepatotoxicity. Furthermore, since a number of patients have been receiving the drug for several months, there is a suggestion of a possible therapeutic effect.

In view of its promise, it seems likely that 17AAG will enter Phase II clinical trials. These will certainly involve both single agent administration and also combination studies. For example, promising results have been obtained in breast cancer models using 17AAG in combination with taxol [45]. Considerably more work needs to be done in order to define optimal schedules and drug combinations.

## 6. Novel Hsp90 drugs

17AAG will continue to undergo clinical evaluation. It is hoped that this first-in-class agent will provide proof of concept for Hsp90 inhibition in the clinic, and may well have sufficient advantages to allow it to progress to regulatory approval. Nevertheless, it possesses several features that can be improved upon. An ideal Hsp90 drug would have better solubility and pharmaceutical properties, which would in turn allow the development of an improved formulation. Oral bioavailability to support the chronic dosing schedules is likely to be needed. Avoidance of the P-glycoprotein efflux pump is desirable and lack of metabolism by the polymorphic cytochrome P450 CYP3A4 would also be an advantage. In addition, it is not clear whether the effects of DT-diaphorase/NQO1 [17] are a good or bad feature; this characteristic could be modified accordingly. Isogenic models for NQO1 expression can be used in the biological test cascade to check for the dependence of activity on this quinone reductase [46]. Thinking further ahead, there is the possibility of discovering Hsp90 inhibitors that deplete a more restricted set of client proteins [11]. This might translate into further improvements in selectivity or could lead to inhibitors that are more specific for particular tumour types. Novel inhibitors will be developed using approaches based on both high throughput screening [47] and structure-based rational design [33].

## 7. Concluding remarks

Clinical trials of 17AAG are providing us with valuable and rapid feedback which we are able to exploit immediately in new drug discovery. In addition, we and others are continuing with a programme of basic molecular and cellular pharmacology studies, designed to understand in greater detail the mode of action of Hsp90 inhibitors, and in particular the downstream consequences of chaperone inhibition. The results from this work will also feed into new drug design. For example, we are beginning to understand the role of specific genes in the mechanism of action of 17AAG [35].

Postgenomic cancer biology is providing us with a wide range of exciting targets and technologies for the development of new drugs. Several examples of mechanism-based drugs acting on cancer genome targets are already in the clinic. Many others are in preclinical development. There is the real prospect of a new era of predictive, individualised therapy, in which patients will be administered a cocktail of agents that target their own particular cancer. Developing such agents does however throw up a number of challenges. Although it is extremely encouraging that single agent activity is being seen with drugs such as the first generation of signal transduction inhibitors, it is likely that combinations of several drugs will be needed in order to maximise the therapeutic effect and to avoid the rapid development of drug resistance. Hsp90 inhibitors such as 17AAG have the major potential advantage of hitting several key oncogenic targets, pathways and features of the malignant phenotype simultaneously with a single drug. However, even this agent is likely to be used in combination with others. The application of pharmacogenomics to new cancer drug discovery should open up a new era of opportunities and challenges over the next 5 years.

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