Stressing the Development of Small Molecules Targeting HSP90

Inhibitors of the molecular chaperone HSP90 have been in clinical development as anticancer agents since 1999. Recent clinical studies, including the work of Saif and colleagues in this issue of Clinical Cancer Research, demonstrate that significant progress has been made in overcoming the obstacles preventing regulatory approval. Clin Cancer Res; 20(2); 1–3. ©2013 AACR.

In this issue of Clinical Cancer Research, Saif and colleagues report the findings of a phase I open-label dose-escalation study of BIIB021 (developed by Biogen Idec after acquisition from Conforma Therapeutics), the first fully synthetic, orally available inhibitor of the molecular chaperone HSP90 (1). As has been the case for other chemically synthetic, non-ansamycin HSP90 inhibitors, BIIB021 was generally well tolerated, and the authors were able to identify a dose and schedule at which pharmacodynamic analysis of tumor tissue and peripheral blood mononuclear cells (PBMC) demonstrated responses consistent with anti-HSP90 biologic activity. As the authors point out, determining target engagement of HSP90 inhibitors in patients is not a straightforward undertaking, as the consequences of HSP90 inhibition are most commonly assessed by either HSP70 induction (in itself likely antagonistic to the antitumor activity of these drugs) or secondary effects on chaperone-dependent client proteins, commonly visualized as markedly reduced protein stability and/or activity (particularly in the case of protein kinases, one of the largest classes within the HSP90 client proteome; ref. 2). Although PBMC are readily obtained, several studies have concluded that although these cells may demonstrate target engagement in the patient at the dose and schedule under evaluation, they are neither a useful tissue surrogate for HSP90 inhibition in tumor nor a reliable predictor of clinical response (3). It is thus significant that Saif and colleagues could demonstrate biologic activity in biopsied tumor tissues at their chosen drug dose and schedule. The authors also propose several additional pharmacodynamic assays to monitor target engagement, including quantification of circulating HSP70 levels and circulating levels of the HER2 extracellular domain (in the context of HER2-positive cancers). The latter approach might also be applicable for monitoring drug activity in cancers expressing high levels of other known HSP90-dependent transmembrane tyrosine kinases, including ALK, EGFR, and MET. In addition, for tumors that are highly glycolytic [e.g., gastrointestinal stromal tumor (GIST)], Saif and colleagues demonstrate that positron emission tomography (PET) imaging of glucose uptake provides a dynamic, noninvasive readout of HSP90 inhibition, in agreement with a study evaluating an ansamycin-based HSP90 inhibitor in patients with GIST (4).

Since the identification, nearly 20 years ago, of the benzoquinone ansamycin antibiotics (including geldanamycin and herbimycin), followed shortly thereafter by the structurally unrelated natural product radicicol, as the first small-molecule HSP90 inhibitors, these bioprobes have not only served as initial templates for drug development but have also proved to be immensely useful reagents to investigate the highly complex nature of HSP90 function in normal and cancer cells (2). To this day, all clinically evaluated HSP90 inhibitors (Fig. 1) share the same binding motif, and all interfere similarly with the nucleotide-driven conformational cycling of HSP90, which is a key requirement for its chaperone activity.

Upon HSP90 inhibition, HSP90-dependent clients undergo chaperone-mediated degradation by proteasomes, with the rate of degradation broadly reflecting the degree of HSP90 dependence. Several highly sensitive HSP90 clients, including HER2, EML4-ALK, and EGFR kinase domain mutants, are known tumor drivers and targeting HSP90 in patients with these cancers (e.g., breast cancer and non–small cell lung cancer) has resulted in clinical responses as defined by RECIST criteria (5). These data have led to the suggestion that client protein sensitivity to HSP90 inhibition may be a key predictor of HSP90 inhibitor clinical efficacy, especially in cases in which the tumor is addicted to the client. As proposed by Saif and colleagues, HSP90 inhibition may also represent an effective strategy to overcome or delay development of tyrosine kinase inhibitor resistance. In addition to the example of drug-resistant BCR-ABL provided by the authors (1), preclinical and...
clinical examples of crizotinib-resistant ALK mutations responding to HSP90 inhibition also have been reported (6, 7). Furthermore, a recent preclinical study demonstrated synergistic growth inhibition in MET-driven tumor models upon combining an HSP90 inhibitor and a kinase inhibitor targeting this HSP90-dependent kinase (8).

In normal cells and tissues, HSP90 broadly functions to maintain protein homeostasis in the face of environmental stress. Cancer cells have taken advantage of this homeostatic function by using HSP90 to promote their ability to cope with numerous stresses, including genotoxic, proteotoxic, and hypoxic insults as well as nutrient deprivation. For example, a recent study identified an HSP90 inhibitor to be among a small group of compounds that demonstrated enhanced cytotoxicity toward aneuploid colorectal and lung cancer cell lines (9). The enhanced sensitivity of aneuploid cancer cells to HSP90 inhibition may reflect elevated proteotoxic stress associated with aneuploidy, in part as a consequence of accumulating misfolded proteins. Supporting this hypothesis, HSP90 inhibitors synergize with proteasome inhibitors in multiple myeloma, a cancer in which the protein homeostatic machinery (including proteasomes) is taxed to the utmost. Combination of an HSP90 inhibitor and the proteasome inhibitor bortezomib was associated with durable responses in heavily pretreated patients with multiple myeloma, including those with bortezomib-refractory disease (10). Supporting a general role for HSP90 in maintaining cancer robustness, two recent studies have correlated high tumor HSP90 expression with poor overall survival in patients with non–small cell lung cancer and breast cancer (11, 12). These observations suggest that HSP90 inhibitors may enhance the effectiveness of other treatment strategies, including chemotherapy and radiation. Numerous preclinical studies support this possibility and warrant further clinical evaluation of appropriate drug combinations (5).

Since 17-AAG entered the clinic as the first-in-human HSP90 inhibitor, 17 agents have been in clinical trials and 9 remain under clinical investigation (Fig. 1). The great potential for HSP90 inhibitors to target cancers driven by HSP90-dependent clients, to reduce the likelihood of escape from targeted tyrosine kinase inhibitors while perhaps synergizing with these agents, and to generally reduce cancer fitness relative to the host, continues to encourage extensive translational drug discovery/development efforts focused on this molecular target, even though an HSP90 inhibitor has yet to be approved for any cancer indication. Currently, HSP90 inhibitors are being evaluated in 38 clinical trials (13), and one drug, ganetesib (STA-9090, Synta), is currently undergoing phase III evaluation (in patients with non–small cell lung cancer treated with docetaxel plus or minus ganetesib). The reemergence of BIIB021 adds an additional, chemically distinct, and well-tolerated HSP90 inhibitor as a viable clinical candidate. Continued improvement in our understanding of HSP90 biology, proceeding apace with
ongoing well-designed clinical studies using the various available HSP90 inhibitors, will be instrumental in leveraging the cancer stress response and insuring the ultimately successful development of chaperone-based anticancer therapy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References

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Conception and design: L. Neckers, J.B. Trepel
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Grant Support
This work was supported by funds from the Intramural Research Program of the National Cancer Institute.

Received October 9, 2013; accepted October 19, 2013; published OnlineFirst October 28, 2013.
Clinical Cancer Research

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Clin Cancer Res Published OnlineFirst October 28, 2013.

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doi:10.1158/1078-0432.CCR-13-2571

Supplementary Material  Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2014/01/20/1078-0432.CCR-13-2571.DC1

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