CHAPTER 13

TARGETING Hsp90 FUNCTION TO TREAT CANCER: MUCH MORE TO BE LEARNED

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Abstract: Molecular chaperones or so-called heat shock proteins act as central integrators of protein homeostasis within cells. Among the major chaperones, however, Hsp90 is unique because it is not required for the biogenesis of most polypeptides. Instead, it oversees a surprisingly diverse network of conformationally labile client substrates that regulate signaling pathways and gene expression. Many of the processes modulated by Hsp90 are dysregulated in cancer cells including cell cycle control, apoptosis and chromatin re-modeling. Over the past decade, much of the progress achieved in understanding the complex role of Hsp90 in cancer biology has been made possible by the discovery of several natural product antitumor antibiotics that selectively inhibit Hsp90 function. These compounds have the ability to accomplish what most molecularly targeted anticancer therapies do not – the simultaneous disruption of multiple processes critical to tumor cell growth and survival. Now, great enthusiasm exists over the prospect of targeting Hsp90 function to treat cancer. New chemotypes with improved pharmacology are being developed and clinical trials have demonstrated that Hsp90 function can be inhibited in cancer patients without undue acute toxicity. Remarkable progress has been made, but much more remains to be learned if we are to succeed in the challenge of defining safe and effective ways to exploit Hsp90 inhibition in the treatment of patients

Keywords: Chaperone, geldanamycin, heat shock protein, chemotherapy

It is much more difficult to be convincing about ignorance concerning disease mechanisms than it is to make claims for full comprehension, especially when the comprehension leads, logically or not, to some sort of action.

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INTRODUCTION

Tremendous progress in understanding the specific molecular genetic lesions that underlie the initiation and progression of human cancers has made possible the development of targeted therapeutics that do not rely on the generalized disruption of DNA metabolism and cell division for their activity. Of particular interest have been inhibitors of cellular signal transduction pathways involving kinases and hormone receptors. Unique within this rapidly expanding array of small molecules and proteins, have been compounds that target the functions of heat shock protein 90 (Hsp90). This multifunctional molecular chaperone regulates the post-translational stability and function of a distinct but diverse set of “client” proteins known to be critically involved in oncogenesis (also See: Pratts et al, Chapter 1, Neckers, Chapter 12, Kamal et al, Chapter 14). Inhibition of Hsp90 leads to depletion of many of these oncogenic clients by stimulating their enhanced degradation by the ubiquitin-proteasome system. Most of the current enthusiasm driving the discovery and development of Hsp90 inhibitors has been generated by their potential to accomplish what many molecularly targeted anticancer therapies do not – the simultaneous disruption of multiple signaling pathways critical to tumor cell growth and survival. Such a combinatorial attack on the oncogenic clients of Hsp90 has been proposed to represent a “rational approach” to addressing the heterogeneity and complexity of the numerous genetic defects characteristic of most clinical cancers. Decades of careful investigation encompassing many different fields has provided a wealth of knowledge about Hsp90 and its interaction with its client proteins. Nevertheless, our understanding of Hsp90 function and how it is altered in various cancers remains far from complete. In particular the impact of altering Hsp90 function on cellular processes other than signaling, such as protein homeostasis, energy metabolism, chromatin re-modeling and DNA repair has been given much less consideration. A better understanding of Hsp90 function at a more global level will be required for understanding its role in oncogenesis and for the efficient development of Hsp90 inhibitors as useful cancer chemotherapeutics Soti, 2005 #739}. In this regard, targeting Hsp90 in the treatment of cancer presents its own unique challenges. But it can also serve as an excellent paradigm for thinking more generally about molecular interventions as “perturbagens” that alter not just their target, but rather the function of entire systems to generate their desired therapeutic effects(Lamb et al., 2006; Ramanathan et al., 2005a).

Interest in Hsp90 inhibition as a therapeutic strategy is high with an average of 5 to 10 new cancer-related research papers appearing each week in PubMed. Academic labs, biotechnology firms and large pharmaceutical corporations are generating a wealth of new compounds with potent and selective Hsp90 inhibitory activity. Many recent reviews are available summarizing the pre-clinical and clinical data generated as these compounds are evaluated (Cullinan and Whitesell, 2006; Goetz et al., 2003; Isaacs et al., 2003; Sharp and Workman, 2006). Here we provide a brief summary of Hsp90 structure and function to provide context and describe some of the more recent progress in identifying and developing new inhibitors of this chaperone. To avoid repetition and provide a somewhat different perspective,