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Review

PU-H71: An improvement on nature's solutions to oncogenic Hsp90 addiction

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Geldanamycin
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17-AAG (17-N-allylamino-17-demethoxygeldanamycin/tanespimycin)
17-DMAG (17-desmethoxy-17-N,N-dimethylaminoethylaminogeldanamycin/alvespimycin)
IPI-504 (retaspimycin)
STA-9090 (ganetespib)
PU3 (9-butyl-8(3,4,5-trimethoxy-benzyl)-9H-purin-6-ylamine)
BIIB021 (6-chloro-9-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-9H-purin-2-amine)
PU-H71 (8-[(6-iodo-1,3-benzodioxol-5-yl)sulfanyl]-9-[3-(propan-2-ylamino)propyl]purin-6-amine)

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ABSTRACT

Despite recent advances in precision medicine, many molecular-based antineoplastic agents do not potentiate sustainable long term remissions, warranting the investigation of novel therapeutic strategies. Heat shock protein 90 (Hsp90) is a molecular chaperone that not only has oncogenic properties, but also has distinct expression profiles in malignant and normal cells, providing a rational strategy to attain preferential damage. Prior attempts to target Hsp90 with natural product-based compounds have been hampered by their associated off target toxicities, suggesting that novel, fully synthetic inhibitors may be required to achieve the specificity necessary for therapeutic efficacy. Therefore, this review highlights the antineoplastic potential of PU-H71 (8-[(6-iodo-1,3-benzodioxol-5-yl)sulfanyl]-9-[3-(propan-2-ylamino)propyl]purin-6-amine), a novel purine based analog that has shown efficacy in many preclinical models of malignancy, and is now under clinical examination. In addition, the review suggests potential concomitant therapeutic approaches that may be particularly beneficial to molecular-based, as well as traditional cytotoxic cancer chemotherapy.

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1. Introduction

The world of antineoplastic drug discovery is changing. Traditionally, agents designed for cancer chemotherapy rely on the principal that malignant cells have higher proliferation rates than normal cells, enabling the selective poisoning of malignant tissue with agents that disrupt vital components of the cell cycle. Specifically, these traditional antineoplastic agents target either nucleic acids and proteins involved in DNA synthesis and transcription, or microtubules responsible for chromosome congression and proper segregation of chromosomes during anaphase [1]. While effective against several hematological malignancies and solid tumors, traditional chemotherapeutic agents are inherently limited by their less than ideal toxicity profiles, producing significant deleterious off target effects in patients that limit dosing schedules. Further, many cancers are refractory or eventually develop resistance to traditional cytotoxic agents, thereby potentiating drug resistant tumors that portend a very poor prognosis.

In recent years, the commendable progress in molecular biology has enabled investigators to probe deregulated signaling pathways and oncoproteins that are imperative for carcinogenesis. This has launched the introduction of precision medicine in cancer chemotherapy in which clinicians now have the capability of selecting optimal therapies based on the genetic and phenotypic profile of the patient's malignancy in addition to traditional broad spanning cytotoxic antineoplastic intervention. Novel targeted approaches, such as hormonal therapy, monoclonal antibodies (mABs) and associated immunoconjugates, and small molecule kinase inhibitors have given clinicians an unprecedented ability to discriminate between neoplastic and normal tissue. Nevertheless, these agents suffer from many of the same pitfalls associated with traditional cytotoxic chemotherapy. Hormonal therapy is limited in the scope of tumors perturbed by such intervention, and such protocols have a low, but notable risk of potentiating other malignancies in addition to inducing an initial surge in tumor growth [2,3]. In the case of immunotherapy, tumors are not homogeneous in their cell surface protein expression, and it is possible that some cells lack the required epitope, or inadvertently shed the required antigen if it is unnecessary for cell survival [4–7]. Kinase inhibitors enable the clinician to select for patient malignancies that rely on specific aberrantly expressed pathways, but are often toxic to normal cells based on the requirement of these signals for homeostatic functions [8,9].

Although the amount of progress cancer chemotherapy has made in recent years is noteworthy, there is an apparent need for chemotherapeutic agents that work by mechanisms not currently approved for clinical use. Recent work has implicated molecular chaperones, ubiquitously expressed proteins vital to the formation of certain macromolecular structures, to be a particularly intriguing target of interest. Molecular chaperones are members of a unique class of proteins that constitute the chaperome, an interconnected network of molecular chaperones, co-chaperones, and folding enzymes encoded by as many as 169 genes that help maintain cell stability by regulating proteome machinery required for a vast array of housekeeping activities [10]. The ubiquitous nature of chaperones initially suggested that the chaperome was of little interest to oncology as such proteins are highly expressed in both normal and malignant cells. However, there exist inherent differences in the expression profile of chaperones under normal conditions and those induced by oncogenic stress [10–12], enabling the targeted inhibition of proteins vital for malignant tissue.

A particular molecular chaperone of interest is heat shock protein 90 (Hsp90), which has been shown to support aberrant expression of key oncoproteins such as ALK (anaplastic lymphoma kinase), BCR-ABL (break point cluster-Abelson tyrosine kinase) BRAF (serine/threonine-protein kinase B-Raf), CDK4 (cyclin-dependent kinase 4), CRAF (serine/threonine-protein kinase C-Raf), HER2 (human epidermal growth factor receptor 2), JAK2 (Janus kinase 2), KIT (Mast/stem cell growth factor receptor, proto-oncogene c-Kit) MET (mesenchymal epithelial transition factor), and STK33 (serine/threonine kinase 33) [13–17]. Initial attempts to target Hsp90 with inhibitors that resemble the structure of the natural products geldanamycin and radicicol indicated that successful targeting of the chaperone could yield therapeutic benefit at the clinical level, but such compounds are plagued by unfavorable toxicity profiles that limit achievable doses [18,19]. Consequently, these lower concentrations are unable to sustain consistent antineoplastic activity, and have limited clinical utility. Nevertheless, structure–activity studies have enabled the design of novel purine-based inhibitors [20–23] that have demonstrated notable specificity toward oncogenic Hsp90. The most promising of these agents, PU-H71, is currently under clinical investigation, and will be discussed at length to demonstrate how rational drug design can potentiate the development of chemotherapeutic agents that are highly potent and selective toward malignant tissue.

2. Structure and function of heat shock protein 90

Hsp90 refers to a subgroup of molecular chaperones that fold client proteins to their active conformation through their ATPase activity, and have a characteristic Bergerat fold (unique structural ATP-binding domain) near the N-terminus. There are four different paralogues of Hsp90, each of which has a distinct cellular location; Hsp90α and Hsp90β in the cytoplasm, gp96 (Grp94, ERp99, or endoplasmin) in the endoplasmic reticulum, and Trap-1 in the mitochondria [22,23]. Hsp90 substrates are regulated by the N-terminal ATPase domain, which binds and hydrolyses ATP to mediate association/dissociation cycles between Hsp90 and client proteins [24,25]. This ATPase activity produces several conformations of Hsp90 based on ATP binding status and whether the nucleotide has been hydrolyzed (Fig. 1). The activity of Hsp90 is further regulated by co-chaperones which aid in the conversion