Chapter 10
Targeting Hsp-90 Related Disease Entities for Therapeutic Development

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Abstract Heat shock protein 90 (HSP-90) has been identified in many disease processes including cancer, neurodegeneration, autoimmune diseases, and cancers. Great effort has been expended in the development of specific inhibitors of the N-terminal and C-terminal domains. Inhibitors of post-translational modification have also been developed. Herein, we explore the available inhibitors and those in development, discuss the relevant disease processes, and examine the pitfalls and promises of targeting HSP-90 for therapeutic intervention.

Keywords Autoimmune disease · Cancer · Diabetes · Heat shock proteins · Neurodegeneration · Therapeutics

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Abbreviations

17-AAG	Tanespimycin
ADME	absorption, distribution, metabolism, excretion
AKT	protein kinase B
b-RAF	B-Raf proto-oncogene
c-RAF	RAF proto-oncogene serine/threonine-protein kinase
CTD	C-terminal domain
DMAG	17-dimethylaminoethylamino-17-demethoxygeldanamycin
ER	endoplasmic reticulum
FKBP	FK506 binding protein
FLT	Fms-like tyrosine kinase
GBase	glucocerebrosidase
HDAC	histone deacetylase
HDACI	HDAC inhibitor
HER	human epidermal growth factor receptor
HIF	hypoxia inducible factor
HOP	HSP70-HSP90 organizaing protein
HSF	heat shock factor
HSP	heat shock protein
HTT	huntington protein
IKK	IkB kinase
JAK	Janus kinase
JNK	c-Jun N-terminal kinases
NF-kB	nuclear factor kappa light-chain enhancer of activated B cells
Nrf	nuclear factor erythroid 2-related factor
NTD	N-terminal domain
RAF	rapidly accelerated fibrosarcoma
RASGRP	RAS guanyl-releasing protein
SAHA	suberoyl anilide hydroxamic acid
STAT	signal transducer and activators of transcription
TPR	tetraotricopeptide repeat
VEGFR	vascular endothelial growth factor receptor

10.1 Introduction

Heat-shock protein 90 (HSP-90) regulates the stability, activation, and degradation of a diverse array of proteins associated with growth, proliferation, and survival (Burlison et al. 2006; Neckers and Ivy 2003; Schopf et al. 2017; Schwock et al. 2008). Thus, it is core to regulation of protein stability and protein-degradation pathways and modulating transcription factors, signaling transduction networks, and kinases (Schopf et al. 2017). It facilitates the survival of cells during stress response and exhibits a pronounced anti-apoptotic and stabilization effect. Thus, HSP-90 has been associated with development and progression of a wide range of pathological conditions including cancers, diabetes, Gaucher disease, neurodegenerative diseases, and autoimmune dysfunction (Hoter et al. 2018; Kasperkiewicz et al. 2011; Lackie et al. 2017; Luo et al. 2010; Rice et al. 2008; Russo et al. 2006; Trepel et al. 2010; Tukaj et al. 2015; Whitesell and Linquist 2005; Yang et al. 2013).

10.1.1 Cancer

A commonality in many human cancers is the overexpression of HSP-90; the drastic two-to-three-fold induction of HSP90 seen in several cancers results in increase stabilization of client proteins (Barrott and Haystead 2013). The pronounced increase of HSP-90 in stress conditions can reach up to 6% of total protein (Prodromou 2016; Taipale et al. 2010). As consequence of increase HSP-90, the stabilization of its client protein results in the protects mutated or up-regulated oncoproteins. The aberrant protection of pro-survival and proliferation-related proteins such as telomerases, B-Raf, Akt, p53, VEGFR, HIF1α, HER-2, tyrosine kinases, steroid hormone receptors contribute to tumorigenesis, metastasis, and invasiveness (Banerji 2009; Beliakoff and Whitesell 2004; Hoter et al. 2018; Jhaveri and Modi 2012; Whitesell and Linquist 2005). As HSP90 acts as a regulator of HSF-1, the major hub of HSF transcriptional expression, HSP90 production causes dysregulation of HSF-1 transcriptional activity which leads to alterations in chaperone expression (Duerfeldt and Blagg 2010).

10.1.2 Neurodegenerative Diseases

HSP-90 works in concert with other chaperone machinery to refold misfolded proteins to prevent toxic accumulation. However, as in the case in various cancers, the stabilization of HSP-90 client proteins can have deleterious consequences outside of the context of normal physiological conditions. The stabilization of proteins associated with diseases results in manifestation of various neurodegenerative disease (Lackie et al. 2017; Luo et al. 2010). The HSP-90 client protein stabilization is a major facilitator for the accumulation of intrinsically disordered proteins (Karagoz et al. 2014; Luo et al. 2010). HSP-90 interacts with and stabilizes Tau, (Dickey et al. 2007; Hoter et al. 2018; Karagoz et al. 2014) a microtubule associated protein that mediates axonal transport. Tau hyperphosphorylation and aggregation is a classical hallmark of Alzheimer's disease; the accumulation is also associated with other neurodegenerative disease such as progressive supranuclear palsy and Pick's disease (Gong and Igbal 2008; Guo et al. 2017; Lee et al. 2001; Shelton et al. 2017). The HSP-90/Tau interface is associated with the neurodegenerative pathologic state and is well explained by enhanced stabilization of hyperphosphorylated Tau, which exacerbates aberrant neural activity seen in tauopathies (Shelton et al. 2017).

The aggregation of intrinsically disordered factors is also associated with Huntington's disease and Parkinson's disease (Lackie et al. 2017; Luo et al. 2010). HSP-90 interacts with Huntington protein (HTT) and leucine-rich repeat kinase 2 (Baldo et al. 2012; Wang et al. 2008). Interestingly, as HSP-90 is an established regulator of HSF-1, evidence suggests that, through the repression of HSP-90, other molecular chaperones systems such as HSP-70 can be enhanced and can facilitate increase neuroprotective function in otherwise pathogenic conditions (Luo et al. 2010).

10.1.3 Gaucher Disease

Gaucher disease is a rare autosomal recessive lysosomal disorder driven by genetic mutations in *GBA* gene encoding the lysosomal enzyme glucocerebrosidase (GCase); the mutations result in metabolic dysfunction and wide-spread organ dysfunction due to effects of the drastic accumulation of GCase substrate (Brady et al. 1966; Hruska et al. 2008; Stirnemann et al. 2017; Yang et al. 2013). The diminished amount of GCase results in the toxic accumulation of the GCase substrate, glucosylceramide (Stirnemann et al. 2017). GBA mutations cause protein misfolding and diminished protein instability resulting in increased retention of GCase in the endoplasmic reticulum (Ron and Horowitz 2005; Stirnemann et al. 2017; Yang et al. 2013). The intrinsic changes in the conformation of mutant GCase results in premature degradation and increased GCase turnover (Yang et al. 2013). HSP-90 is critical for targeting misfolded GCase for proteasomal degradation and directly interacts with GCase to direct the misfolded GCase to cellular ER and proteasomal degradation pathway (Yang et al. 2013). The increase degradation of GCase results in enhanced disease severity. This paradigm is in contrast with other diseases associated with HSP-90, as the interaction does not enhance the accumulation of its client protein but rather directs the client protein for degradation.

10.1.4 Diabetes and Associated Complications

Several of the key players mentioned above constitute a regulatory pathway for insulin sensitivity. Transcription of HSP-70 is regulated by HSF-1, which in turn is activated by inhibition of HSP-90 (Lee et al. 2013). Further, inhibition of HSP-90 leads to inhibition of JNK1 and thus improved insulin signaling; in the mouse model in this study, HSP-90 inhibition reversed hyperglycemia (Lee et al. 2013). In another study of diabetic mice, inhibition of HSP-90 with 17-dimethylaminoethylamino-17-demethoxygeldanamycin (DMAG) lessened renal damage and atherosclerosis incurred by hyperglycemia and hyperlipidemia as evidenced by decrease in albuminuria, renal lesions, and proinflammatory genes (Lazaro et al. 2015). Further study of diabetic atheroprotection with DMAG in a diabetic mouse model found

HSP-90 inhibition to be protective by induction of nuclear factor erythroid-derived 2-like (Nrf2) (Lazaro et al. 2017). Hypercoagulability in diabetes was found to be dependent on a glucose-regulated interaction between HSP-90α and annexin II, which promotes the generation of plasmin (Lei et al. 2004).

10.1.5 Autoimmune Disease

HSP-90 machinery is involved in adaptive and innate immune responses via mediating the activation of immune cells (Srivastava 2002; Taipale et al. 2010). It is instrumental in the function of natural killer cells, macrophages, lymphocytes, dendritic cell maturation, neutrophils (Kasperkiewicz et al. 2011; Srivastava 2002). The chaperone has been implicated in inflammation, antigen presentation, and immune cell activation (Srivastava 2002; Taipale et al. 2010). Client proteins of HSP-90 include inflammation regulating kinases IKK and JAK (Madrigal-Matute et al. 2010; Prodromou 2016; Zhang and Burrows 2004). These kinases modulate transcriptional regulators STAT and NF-kB which in turn dictate the expression of many pro-inflammation factors (Madrigal-Matute et al. 2010; Prodromou 2016). Thus, mounting evidence has demonstrated the importance of HSP-90 in regulating pro-inflammation responses and immune cell leading to the hypothesis that HSP-90 plays a critical function in auto-immune disease (DeBoer et al. 1970; Madrigal-Matute et al. 2010; Ron and Horowitz 2005; Stebbins et al. 1997). In support of this hypothesis, studies have implicated HSP90 in autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, allergic rhinitis, and other autoimmune diseases such as bullous skin diseases (Kasperkiewicz et al. 2011; Rice et al. 2008; Russo et al. 2006; Srivastava 2002).

10.2 Targeting HSP-90

10.2.1 Modulating HSP90 Function by Perturbation of PTMs

The post-translational modifications of HSP-90 alter the chaperone dynamics and perturbs the interaction with co-chaperones, substrates, and can influence enzyme activity (Jackson 2012; Kekapure et al. 2009; Scroggins et al. 2007). Acetylation of HSP-90 at the middle domain results in a marked decrease in its function by impeding the ability to interact with co-chaperones and client proteins, changing the dynamic conformation cycles (Aoyagi and Archer 2005; Kovacs et al. 2005; Mollapour and Neckers 2012; Scroggins et al. 2007). Targeting acetylation presents an avenue to modulate the activity of HSP-90. Reversible protein acetylation regulates a wide range of biochemical processes involving HSP-90 (Kovacs et al. 2005; Yu et al. 2002). The inhibition of histone deacetylase induces hyperacetylation HSP-90; the acetylated form of the chaperone has decreased affinity for ATP and target proteins (Bali et al. 2004). HDAC, while traditionally defined by their role in deacetylation of histones, have been found to act on a larger range of substrates including HSP-90 (Bali et al. 2004; Fiskus et al. 2007). Additionally, HDAC have been found to influence drug resistance to chemotherapeutics and diverse HSP90 inhibitors (Chai et al. 2017; Wang et al. n.d.). Interestingly, HDAC proteins such as HDAC6 also regulate the interactions with HSP90 and HSF master regulator, thereby affecting the transcriptional network of other HSP systems (Boyault et al. 2007; de Zoeten et al. 2011; Prodromou 2016).

Inhibiting deacetylation through HDAC inhibitors (HDACI) presents a promising avenue in which HSP90 chaperone cycling and function can be impeded. Ultimately, HDAC influences the stability of a plethora of downstream targets of HSP-90. HDACI have anti-tumorigenic properties correlating with diminished accumulation of HSP-90 target proteins related to pro-survival and pro-growth (Bali et al. 2004; Ding et al. 2017; Park et al. 2008). The inhibition of HSP-90 chaperone function by HDACIs results in degradation of oncoproteins such as AKT, FLT-3, BCR-ABL, RAF-1, VEGFR1, VEGFR2, JAK2, RASGRP1 and CRAF (Bali et al. 2004; Ding et al. 2017; Park et al. 2008). The resulting degradation of the oncoproteins by HSP-90 stabilization leads to dramatic changes in cell cycle control and proliferation. Modulating HDAC6 and HSP90, through HDACI has been studied in the context of ameliorating autoimmunity by affecting T-regulatory cells (Chiosis et al. 2001). Additionally, NF-κB function is impaired by HDACI inhibition of HDAC6. It is thought that the increase in the acetylation of HSP90 results in reduced stability and degradation of IKK. The reduced stability of IKK in turn causes aberrant NF-κB function (Kovacs et al. 2005; Regna et al. 2015; Trepel et al. 2010). Thus, the HDAC/HSP-90 interface presents a promising target to impede autoimmunity. While initial findings in autoimmunity have shown that targeting HDAC6 show some diminished HSP90 function, further studies are needed (Regna et al. 2015).

HDACI can also promote the stability of HSP90 proteins. In the case of Gaucher's disease, the production of mutated GCase results reduced of accumulation of the enzyme through HSP-90-directed degradation (Wang et al. 2008). HDACI, such as LB-205 and SAHA, results in increase acetylated form of HSP-90 and impairs the binding of HSP-90 to GCase (Yang et al. 2013). The increase in the accumulation of the mutated GCase in part increases the functional activity of the GCase thereby limiting toxic accumulation of the GCase substrate, glucosylceramide (Yang et al. 2013).

10.2.2 Targeting HSP-90 C-terminus

While traditional targeting of HSP-90 for therapeutics have predominantly developed to target the N-terminal domain (NTD) of the protein, novel approaches act to impede the C-terminal function of HSP-90. Inhibition of HSP-90 activity through the NTD perturbs the repressive effect of HSP-90 on HSF-1 which subsequently activates heat shock response. The activation of the heat shock response is thought to facilitate resistance which dampens the effect of HSP90 inhibitors (Yang et al. 2013). Therefore, a major driving force of targeting C-terminus is that prior trials with N-terminal targeting small molecules result in rapid development of resistance to the inhibitory molecules (Donnelly and Blagg 2008; Solárová et al. 2015).

The C-terminal inhibitors are subdivided into two categories; inhibitors that directly target the C-terminus and inhibitors that disrupt the binding of HSP90 to co-chaperones at the C-terminus (Koay et al. 2016). Similar to the NTD, the CTD contains a nucleotide binding site, however, lacks ATPase activity (Schopf et al. 2017). While the nucleotide binding site differs in terms of binding affinity and binding specificity, selective targeting of the nucleotide binding site has shown promising applications in inhibiting chaperone function (Donnelly and Blagg 2008; Solárová et al. 2015). Coumarin-based antibiotics were among the first inhibitors found to target the CTD (Solárová et al. 2015). Initially, this class of small molecules were found to inhibit the ATPase activity of ATP-gyrases; further biochemical classification has shown weak affinity towards the nucleotide binding site of CTD (Burlison et al. 2006; Donnelly and Blagg 2008; Solárová et al. 2015). The binding of novobiocin, coumarin-antibiotic, indeed affects the stability of HSP-90 client proteins and prompted the development of synthetic derivatives of the substrate. These nucleotide binding inhibitors induce conformational changes thought to impede and release protein-interaction by disrupting the dimerization of HSP-90 (Allan et al. 2006; Gormley et al. 1996; Solárová et al. 2015).

Novobiocin exerted anti-tumorigenic properties towards certain cancer lines; however, it lacked the efficacy that N-terminal inhibitors showed. Development of synthetic novobiocin derivatives sought to amend the poor efficacy by improving HSP90 inhibition. KU174, and KU675 analogues of novobiocin have shown strong anti-proliferation activity towards prostate cancer lines (Eskew et al. 2011; Liu et al. 2015; Solárová et al. 2015). Other novobiocin analogues developed have shown potential neuroprotective properties and provide an avenue in which HSP-90 inhibitors can be studied in the context of neurodegeneration (Donnelly and Blagg 2008).

Additional molecules have been tested and developed to target the nucleotide binding site of the CTD. These small molecules include the recent discovery of dihydropyrimidinone and analogs of bisphenol A such as NSC145366 as novel classes of CTD binding compounds (Goode et al. 2017; Terracciano et al. 2018). While, their therapeutic potential has not been fully explored, the continual development of CTD inhibiting agents provides an avenue in which HSP-90 can be inhibited without the potential drawback of driving drug resistance. Current research is focused on the neuroprotective properties of dihydropyridine derivatives and may be candidate therapeutic molecule for Alzheimer's disease (Roe et al. 2018). Recently, a novel C-terminal targeting hexapeptide, amioxyrone, was found to bind to specifically target CTD and inhibit dimerization (Bhatia et al. 2018). The targeting of CTD results in the reduced stabilization, downregulation, and degradation of HSP-90 client oncoproteins without the induction of the heat shock response (Bhatia et al. 2018). The hexapeptide showed effectiveness in leukemic cell lines and leukemia stem cells which demonstrated a novel approach in targeting chronic myeloid leukemia (Bhatia et al. 2018).

The alternative strategy of affecting the C-terminal function is by utilizing small molecules that disrupt the binding of HSP90 to co-chaperones. The C-terminal domain of HSP-90 possess MEEVD residue that regulates the interactions with TPR domain containing co-chaperones (Buchner 1999; Wandinger et al. 2008). TPR co-chaperones have tremendous importance in HSP-90 regulation (Schopf et al. 2017). These chaperones modulate the conformation of HSP-90 and interactions with co-chaperones; therefore the HSP90 chaperone machinery is affected (Schopf et al. 2017). While no natural inhibitors have been discovered to target the MEEVD region, exploration of the TPR-domain binding interface has led to the development of synthetic molecules to target the HSP-90-TPR binding interface (Sidera and Patsavoudi 2014). Recently, C-terminal modulators including modified variants of SM molecules: SM122, SM145, SM253, and SM258, have been developed to interact with Hsp90 and block the binding of TRR-domain containing co-chaperones (Koay et al. 2016). These SM molecules disrupt TRR-containing proteins, FKBP52 and HOP (Koay et al. 2016).

10.2.3 Targeting HSP90 N-Terminus

The inhibition of HSP-90 at the N-terminus can be divided into geldanamycin/ geldanamycin derivatives and purine-based inhibitors. The classic targeting of HSP-90 began with the natural analogs geldanamycin, herbimycin, and macbecin (DeBoer et al. 1970). Out of these three, geldanamycin was the most potent inhibitor due to its ability to more effectively bind to the NTD of HSP-90 and prevent ATP binding to the pocket; it also functioned to inhibit HSP-90 dimerization with heat shock factor 1 (HSF-1) which lead to heat shock response through transcriptional activation of factors such as HSP27, HSP40, HSP70, and HSP90 (Zou et al. 1998). The carbamate group of geldanamycin represents one of its core interacting domains with HSP-90 as it may form a hydrogen bonding network within the pocket and elimination of which abolished geldanamycin function (Stebbins et al. 1997).

The major weaknesses of geldanamycin, however, is its low solubility, difficulty in crossing the blood-brain barrier, and most important of all, its induction of the heat shock response from inhibiting HSP-90. This response is comprised of the cells upregulating transcription of heat-shock proteins to properly compensate for the disruption of protein folding (Sittler et al. 2001). To account for the problems associated with geldanamycin, a semi-synthetic derivative of geldanamycin called tanespimycin (17-AAG) was created that improved the ADME activity while decreasing the toxicity and heat shock response generated by geldanamycin (Goetz et al. 2003). As a result, 17-AAG provided a stronger candidate for HSP-90 inhibition. Despite the improvements made by 17-AAG, induction of the heat shock response and resulting toxicity lead to the computer screening of multiple compounds targeting the NTD to develop new compounds that limited the harmful effects of the previous generation of NTD- targeting inhibitors (Table 10.1).

Table 10.1 HSP90 Inhibitors are categorized by mechanism of action

Main molecular mechanism	Inhibitor	Class of inhibitor	Additional molecular mechanisms	Disease	Findings related to therapeutics
Binds to the ATP-binding pocket of Hsp-90	Geldanamycin	Marcolactams/ benzouinone	Affects virion binding of endoplasmin	Kidney cancer, peripheral nerve damage	Inhibits cell growth and promotes cell death of tumor cells
	Retaspimycin	Macrolactams		Cancer	Inhibits cell growth and promotes cell death of tumor cells
	Tanespimycin (17-AAG)	Macrolactams		Lymphoma, sarcoma, leukemia, prostate cancer	Inhibits tumor cell growth and promotes tumor cell death
	Radicicol	Hydroxygenzoic acid derivatives	Affects virion binding of endoplasmin; affects dihydrolipoyllysine-residue acetyltransferase activity of pyruvate dehydrogenase complex; affects pyruvate dehydrogenase kinase activity of pyruvate dehydrogenase lipoamide kinase isozyme 1; prevents p23 from associating with Hsp90;binds to and inhibits DNA topoisomerase type II proteins and GRP94	Malaria, fungus, viral infection, bacterial infection, cancer	Antibiotic, antimalarial, antifungal, antiangiogenic, antiviral, anti-inflammatory properties; decreased levels of progesterone receptor, Raf-1, p185erb82, and mutant p53; **M2-macrophage phenotype inhibition**
	BIIB021	Purines and purine derivatives		Cancer lymphoma	Inhibits tumor cell growth and promotes tumor cell death
	NVP-BEP800	2-Aminothieno[2,3-*d*] pyrimidine		Breast cancer, cancer	Inhibits tumor cell growth and promotes tumor cell death
	CUDC-305	Imidazopyridine		Cancer	Inhibits tumor cell growth and promotes tumor cell death

(continued)

Table 10.1 (continued)

Main molecular mechanism	Inhibitor	Class of inhibitor	Additional molecular mechanisms	Disease	Findings related to therapeutics
	XL888	Tropane alkaloids		Cancer melanoma	Inhibits tumor cell growth and promotes tumor cell death
	AT13387	Isoindoles		Tumor, gastrointestinal tumor	Inhibits tumor cell growth and promotes tumor cell death
	Tanespimycin (17-AAG)	Alpha amino acid esters		Cancer	Inhibits tumor cell growth and promotes tumor cell death
Antagonizes zinc ion binding of protein S100-A12 and S100-A12	Amlexanox	Chromeno[2,3-b] pyridine-5-ones	Inhibitor of fibroblast growth factor-1 S100 protein binding;antagonizes interleukin-3 receptor binding	Aphthous ulcers	Inhibits slow-reacting substance of anaphylaxis;stabilizes fibroblast growth factor 1
Inhibits voltage-gated potassium channel activity of calcium-activated potassium channel subunit alpha-1	Cromoglicate	Chromones	Antagonizes magnesium ion binding of protein S100-P	Allergic rhinitis	Inhibits mast cell degranulation through preventing release of slow-reacting substance of anaphylaxis and histamine; attenuates inflammatory leukotriene release
Increases binding of HSP70 to HSP90 and p23 dissociation from HSP90 complex	NVP-AUY922	Phenylpropanes		Cancer	Inhibits proliferation of multiple human cancer cell lines in-vitro
Inhibits binding of bRD to HSP90-alpha	KW-2478	Antineoplastics		Multiple myeloma, cancer	

The class of inhibitor and applicable disease are also listed. Several classes of inhibitors have additional mechanisms of action

Purine-based inhibitors were a completely synthetic class of HSP-90 inhibitors designed to target the ATP-binding pocket of the NTD created from the complete crystal structure of HSP90 ATP/ADP complex (Prodromou et al. 1997). These inhibitors have increased potency so that side effects associated with the geldanamycin analogs would be minimized at therapeutic doses. Through screening processes, many derivatives of these purine-based inhibitors were created, the first of which was PU3. This derivative mimicked the binding of ATP in the NTD pocket in its closed conformation (Chiosis et al. 2001). The discovery of PU3 opened the door for a HSP90 NTD inhibitors that could potentially be brought through clinical trials due to the decreased toxicity.

Currently, couple of these purine and purine-like inhibitors are undergoing clinical trials. BIIB021 is a member of the purine inhibitors being used to treat chronic lymphocytic leukemia and in a combination trial to treat HER2 (+) metastatic breast cancer (Table 10.1). Frequent grade 3 and 4 toxicities are associated with its use in chronic lymphocytic leukemia such as fatigue and hyponatremia while diarrhea, partial seizure, and nausea have been associated with its use in metastatic breast cancer (Elfiky et al. 2008). Subsequently, this lead to the use of BIIB021 use in gastrointestinal stromal tumor treatment refractory to imatinib and sunitinib where it was well-tolerated and showed metabolic changes in the patients that primarily lead to the stabilization of the tumors (Dickson et al. 2012).

Another major compound of interest is PU-H71, another purine class inhibitor shown in preclinical studies to be effective against breast cancer, hepatocellular carcinoma, and Bcl-6-dependenet diffuse B-cell lymphoma cell lines. Human studies focused on patients with advanced refractory cancers revealed that PU-H71 was well-tolerated, but its discontinuation of supply did not allow a strong therapeutic index to be determined; Evidence suggested stability of disease as the average response (Speranza et al. 2018).

10.3 Conclusions

Herein, we have examined the role of HSP-90 in several disease entities and the routes that have been examined for therapeutic development. Historically, the C-terminal domain and PTM inhibitors have shown the most promise. Future directions will likely focus on combining these inhibitory steps and perhaps developing conjugated inhibitors to bolster delivery and efficacy.

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